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CHEMICAL CHANGES IN THE BLOOD DURING FASTING IN THE HUMAN SUBJECT*

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Although there have been extensive studies of the metabolism of fasting men and animals, as revealed by examinations of the urine and the expired air, comparatively little has been written concerning alterations in the concentration of various chemical constituents of the blood. During the last three years we have conducted thirty fasting periods in which we have measured various blood constituents. The most striking alteration of the blood was found to be a greatly increased concentration of uric acid. This observation, together with a study of the factors affecting uric acid retention during fasting, has been published.[1] This article deals with observations on the concentration in the blood of nonprotein, urea and amino-acid nitrogen, sugar, cholesterol, fibrin, inorganic phosphorus, total calcium and plasma bicarbonate. Observations concerning chlorides will be presented elsewhere.

MATERIAL AND METHODS

Of the thirty fasting periods, twenty-four were of persons who were fasted as a therapeutic measure for the relief of convulsions. The remaining six periods were of two healthy persons who acted as normal controls. Of the twenty-four subjects studied, two-thirds were male and one-third female. Ages ranged from 13 to 42 years. A series of

* From the laboratory of the department of neuropathology, Harvard Medical School, the medical service of the Massachusetts General Hospital and the Thorndike Memorial Laboratory of the Boston City Hospital. This research was made possible through a grant by the Committee on Epilepsy, New York City. This paper is no. 50 in a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

† Fellow in Medicine of the National Research Council during the greater portion of this research.

1. Lennox, W. G.: Increase of Uric Acid in Blood During Prolonged Starvation, J. A. M. A. **82**:602 (Feb. 23) 1924; J. Biol. Chem. **66**:521 (Dec.) 1925.

observations, published [2] and unpublished, has shown that the blood of persons subject to convulsions contains normal amounts of sugar, of bicarbonate and of the nonprotein nitrogenous constituents. We believe that in the main the alterations in blood chemistry, which we will describe, have nothing to do with the tendency toward convulsions which these patients exhibit, but are normal physiologic adjustments to fasting. Possible exceptions to this rule will be pointed out later.

TABLE 1.—*Measurements of Nonprotein Nitrogen of Blood During Fasting*

		Subjects										
		1 (first)	1 (second)	2	3	4	5	6	7	8	9	10
Diet	Day	Mg. per 100 Cc. of Whole Blood										
Food	1	....	....	....	35.2	....	....	....	....	38.7	....	....
	2	....	....	....	37.7	....	31.6	....	....	37.5	....	....
	3	....	....	....	36.8	....	42.0	....	33.4	39.3	....	....
	4	39.4	....	....	34.8	41.0	35.9	....	34.3	35.3	32.8	30.3
Fast	1	30.9	44.0	....	....	38.0	39.2	....	....	43.5	....	26.7
	2	....	33.8	....	....	44.0	30.4	31.6	34.7	42.2	30.6	40.3
	3	35.5	....	41.8	52.2	40.0	35.2	33.4	45.4	....	41.1	38.7
	4	....	....	34.2	....	....	....	32.1	48.2	....	35.3	34.3
	5	31.5	45.2	33.0	39.7	....	29.8	34.3	48.0	44.4	38.7	33.3
	6	....	....	40.5	....	....	37.3	32.5	41.3	42.2	31.8	35.7
	7	36.8	39.2	40.5	32.1	42.2	37.3	34.0	41.3	40.0	35.7	30.2
	8	....	....	....	34.9	37.0	37.7	37.0	40.8	35.4	28.9	26.7
	9	....	....	....	....	39.2	33.5	36.2	41.3	39.5	36.4	33.3
	10	36.3	33.3	....	37.5	37.7	29.7	35.7	36.4	40.0	29.7	30.1
	11	....	30.5	37.4	....	28.2	25.6	31.9	34.9	46.2	34.7	26.8
	12	35.1	....	35.1	32.4	....	....	31.6	32.4	44.4	33.5	24.4
	13	....	....	....	....	37.0	....	37.5	40.0	30.0	38.9	24.6
	14	28.5	37.5	28.5	....	31.9	....	32.5	41.4	33.3	....	....
	15	....	....	40.5	....	26.6	24.0	....	....	28.6	....	....
	16	....	50.0	....	....	....	....	....	....	....	....	....
	17	27.8*	....	....	....	....	....	....	....	....	....	....
	18	....	54.5	....	....	....	....	....	....	....	....	....
	20	....	38.0	....	....	....	....	....	....	....	....	....
	21	....	27.9	....	....	....	....	....	....	....	....	....
Food	1	29.2	30.0	40.4	37.9	27.8	25.5	33.4	42.8	37.5	41.1	26.8
	2	35.4	31.2	30.0	24.5	31.9	26.1	33.7	....	38.0	....	21.3
	3	35.2	....	37.7	28.5	30.6	28.6	33.9	....	38.7	31.6	....
	4	31.1	....	30.6	20.6	28.4	24.0	35.3	....	32.4	28.6	....
	5	....	....	30.0	21.6	31.3	26.0	25.2	....	....	....	....
	6	....	....	28.2	27.2	27.9	27.5	....	....	29.3	....	....
	7	....	....	28.8	32.6	38.7	....	....	....	....	....	....
	8	....	....	32.4	27.8	33.0	....	....	....	....	....	....
	9	....	....	28.0	30.4	33.7	....	....	....	....	....	....
	10	....	....	31.6	26.1	33.9	....	....	....	....	....	24.6
	11	....	....	30.0	31.4	32.7	....	....	....	....	....	....
	12	....	....	29.2	33.3	40.8	....	....	....	....	....	....
	13	....	....	....	29.2	42.0	....	....	....	....	....	....
	14	....	....	....	31.6	38.7	....	....	....	....	....	....

* In this and subsequent tables, the last measurement recorded during fast marks the end of the fasting period.

Fasting periods varied in length from three to twenty-one days. The usual length was fourteen days. Except in a few instances, water intake was unlimited. In some periods, as will be noted in the tables, certain substances were given during fasting in order to study the effect on uric acid retention. All patients except one, patient 4, were confined to the ward during fasting. The healthy subject (subject 11) continued

2. Lennox, W. G.; Wright, L. H., and O'Connor, M. F.: Arch. Neurol. & Psychiat. **11**:112 (Jan.) 1924.

his usual laboratory work. Unless otherwise noted, fast was broken by means of mixed, purine free, low protein diet. Before and after the period of fast, blood was drawn in the morning before breakfast. Approximately 20 cc. was taken daily. It is not probable that withdrawal of this small amount influenced the concentration of the constituents studied. There was no significant decrease in the percentage of hemoglobin. Observations by Dr. H. S. Forbes at the end of a fifteen day fast of patient 4 showed no increase in the number of reticulated red cells.

The following methods of analysis were used: blood nonprotein and urea nitrogen, Folin-Wu;[3] amino-acid nitrogen, Folin;[4] sugar, Folin-Wu;[5] calcium, Kramer and Tisdall;[6] inorganic phosphate, Bell and Doisy;[7] cholesterol, Bloor;[8] plasma bicarbonate, Van Slyke;[9] fibrin, Foster and Whipple.[10]

NONPROTEIN NITROGEN

Table 1 gives the measurements of nonprotein nitrogen during and subsequent to eleven fasting periods. Inspection of the table shows for most of the periods, variable values from day to day, with a tendency toward higher measurements during the fasting periods. Only a few of these measurements, however, were abnormally high. Increases, when they occurred, were transient. Thus, during the second fast of patient 1, nonprotein nitrogen per hundred cubic centimeters of blood was 54 mg. on the eighteenth day, and 28 mg. on the twenty-first day. These fluctuations are presumably explained by uneven catabolism of body protein. The fact that the level of circulating nitrogen may vary so greatly from day to day suggests that the amount of nitrogen excreted daily may not exactly measure (as it has been assumed to do) the amount of protein being catabolized in the body. In other words, small variations in nitrogen excretion may be merely the reflection of variations in the level of circulating nitrogen in blood and tissues.

In the period of refeeding subsequent to fasting there was in almost all cases a definite decrease in the level of nonprotein nitrogen in the blood. The question arises whether such decrease was due to increased elimination of nitrogen or to increased synthesis of nitrogen by the tissues. In a person weighing 70 Kg. a decrease of nonprotein nitrogen

3. Folin, O., and Wu, H.: J. Biol. Chem. **38**:81 (May) 1919.
4. Folin, O.: J. Biol. Chem. **51**:377 (April) 1922.
5. Folin, O., and Wu, H.: J. Biol. Chem. **41**:367 (March) 1920.
6. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.
7. Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.
8. Bloor, W. R.; Pelham, K. F., and Allen, D. M.: J. Biol. Chem. **52**:191 (May) 1922.
9. Van Slyke, D. D.: J. Biol. Chem. **30**:347 (June) 1917.
10. Foster, D. P., and Whipple, G. H.: Am. J. Physiol. **58**:365 (Jan.) 1922.

of 20 mg. per hundred cubic centimeters of blood, if it were excreted in the urine, would increase the total urinary nitrogen by approximately 1.3 Gm. In several instances we found that coincidently with the resumption of food, and the reduction in nonprotein nitrogen in the blood, less nitrogen was excreted than was ingested. It would seem probable, therefore, that the nonprotein nitrogen which leaves the blood after fasting is not excreted but is used in building body protein.

TABLE 2.—*Measurements of Urea and Amino-Acid Nitrogen of Blood During Fasting*

		Subjects					
		2		3		1 (first)	
		Mg. per 100 Cc. of Whole Blood					
Diet	Day	Urea Nitrogen	Amino-Acid Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen
Food.....	1	....	...	16.6	6.5	....	...
	2	....	...	15.3	6.6	....	...
	3	....	...	14.6	7.1	....	...
	4	....	...	14.3	6.2	....	...
Fast.....	1	....	...	....	...	....	..
	2	....	...	....	...	....	...
	3	16.4	6.6	21.7	6.1	17.6	6.3
	4	13.6	6.5	....	...	....	...
	5	13.0	6.1	....	6.4	13.0	6.3
	6	17.6	6.0	....	...	....	...
	7	17.5	5.3	....	6.7	15.8	5.5
	10	....	...	15.8	6.4	15.0	6.8
	11	....	7.2	....	...	....	...
	12	....	6.2	13.3	6.1	14.2	6.5
	13	....	...	....	...	....	...
	14	15.0	5.8	....	...	11.5	6.5
	17	....	..	....	...	9.5	6.2
Food.....	1	16.4	5.8	13.1	5.3	8.8	...
	2	15.3	6.5	8.8	6.5	10.8	5.3
	3	15.8	...	9.8	5.8	11.5	6.5
	4	12.0	7.3	8.3	6.1	....	5.2
	5	13.9	5.9	11.2	5.6	....	...
	6	13.0	6.1	12.5	5.9	....	...
	7	15.0	5.1	15.0	5.4	....	...
	8	15.0	5.4	11.7	6.1	....	...
	9	11.2	5.3	....	6.3	....	...
	10	14.3	5.2	....	6.2	....	...
	11	14.4	5.5	....	7.2	....	...
	12	11.7	6.7	15.4	6.8	....	...

UREA AND AMINO-ACID NITROGEN

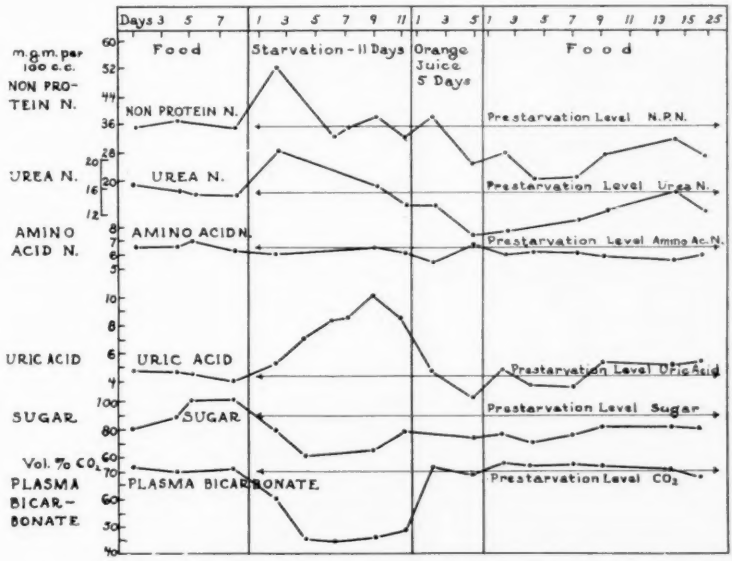
Table 2 shows that the concentration of urea nitrogen during fasting behaved in the same manner as nonprotein nitrogen. In contrast, the amino-acid nitrogen remained remarkably constant, both throughout fasting and the subsequent period of refeeding. From measurements of the amino-acid nitrogen of the blood, we would never suspect that profound metabolic disturbances of the body were in progress. The constancy of the level of amino-acids in the blood during fasting is in agreement with observations of their normal concentrations in a variety of diseases [11] and under various experimental conditions.[12]

11. Greene, C. H.; Sandiford, K., and Ross, H.: J. Biol. Chem. **58**:643 (Jan.) 1924.

12. Okada, S., and Hayashi, T.: J. Biol. Chem. **51**:121 (March) 1922.

The accompanying chart presents a comparison of various chemical constituents of the blood during the fast of patient 2. It will be noted that nonprotein and urea nitrogen concentrations ran parallel, that amino-acid nitrogen remained constant, and that uric acid increased without reference to the other nonprotein nitrogenous constituents.

Observations detailed in tables 1 and 2 were made at intervals of from one to several days. Table 3 gives measurements at short intervals (from four to twelve hours) during three fasting experiments of healthy subject 11. In the first fast the greatest variation in concentra-



Comparison of the concentration of nonprotein, urea and amino-acid nitrogen, uric acid, sugar and plasma bicarbonate in patient 3 during and subsequent to fasting.

tion was 13 mg. for nonprotein nitrogen and only 0.6 mg. for amino-acid nitrogen. During the second and fourth fasts undertaken by this subject, variation in nonprotein nitrogen was not so great, a fact observed by Morgulis and Edwards [13] during a second fast of a dog.

Table 4 presents a comparison of all the nonprotein nitrogenous constituents on the twenty-first day of fasting of subject 1 in comparison with two days after the resumption of a low protein, purine free diet. In the two samples total nonprotein nitrogen was the same. At

13. Morgulis, S., and Edwards, A. C.: Am. J. Physiol. **68**:477 (May) 1924.

the end of the fast uric acid and rest nitrogen were higher, and urea, amino-acid and creatinine lower than two days later.

There are few published observations that are strictly comparable to our own. Morgulis and Edwards [13] measured the nonprotein nitrogenous constituents in the blood of seven dogs during and subsequent

TABLE 3.—*Measurements of Nonprotein Nitrogen of Blood at Short Intervals During Three Fasts of Healthy Subject 11*

Blood Sample	Amino-Acid Nitrogen, Mg. per 100 Cc. of Whole Blood	Nonprotein Nitrogen, Mg. per 100 Cc. of Whole Blood		
	First Fast	First Fast	Second Fast	Fourth Fast
1	...	28.6	37.4	34.3
2	5.5	31.6	36.8	30.3
3	5.0	28.3	35.3	30.4
4	5.1	30.3	33.9	33.4
5	5.1	30.0	34.3	31.6
6	5.6	31.9	34.3	34.3
7	5.3	36.8	34.7	28.6
8	5.5	35.3	37.0	42.3‡
9	5.1	39.5	36.4	33.2
10	5.3	40.3	35.3	38.5
11	5.6	41.2	35.3	46.2‡
12	5.0	40.0	37.4	32.2
13	5.8	43.5	34.5	36.8
14	...	....	33.4*	34.3
15	...	....	34.9	34.9
16	...	....	33.2	....
17	...	....	33.7	....
18	...	....	33.4	....
19	...	...	30.8	....
20	...	....	33.4	....
21	...	....	32.1†	....
22	...	....	35.8	....
23	...	....	31.6	....
24	...	....	30.4	....

First fast, duration fifty-four hours. Blood taken at four hour intervals throughout. Last sample taken two and one-half hours after food.

Second fast, duration four days. Blood taken at intervals of from two to twelve hours.

* Seventy-five grams of soda bicarbonate taken during subsequent twenty-four hours.

† Beginning of mixed diet.

Fourth fast, duration seven days. Blood taken three to five times a day.

‡ Blood taken several hours after ingestion of 25 Gm. of asparagine and 85 Gm. of protein, respectively.

TABLE 4.—*Constituents of Blood on Twenty-first Day of Fast and Two Days After Resumption of Food (Second Fast of Subject 1)*

Diet	Mg. per 100 Cc. of Whole Blood							
	Non-protein Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen	Uric Acid Nitrogen	Creat-inine Nitrogen	Creatine Nitrogen	Rest Nitrogen	Sugar
Last (21st) day of fasting.....	27.9	12.9	5.9	3.3	0.71	0.9	4.2	62
After two days of food*.....	27.1	14.3	8.1	1.1	0.46	1.2	1.9	95

* Blood taken eighteen hours after food.

to fasting. Their dogs were fasted till they lost approximately 40 per cent of their body weight, whereas the majority of our subjects lost only about from 10 to 15 per cent of their initial weight. During this stage of 10 per cent loss, Morgulis and Edwards, in order to avoid changes due to anemia, drew blood from their dogs but once. Haden

and Orr [14] made daily measurements during an eleven day fast of a single dog. Hoeffel and Moriarty [15] have published observations on three fasting children and Harding and associates [16] on a group of patients fed on a low caloric high fat diet. Though our material and methods differ somewhat from those used by these writers, our results are in substantial agreement with theirs.

SUGAR

In the eight fasts tabulated in table 5, the level of sugar in the blood declined during the first week of fasting, after which it rose to nearly its prefasting level. The curves for blood sugar and plasma bicarbonate

TABLE 5.—*Measurements of Sugar of Blood During Fasting*

		Subjects									
		11			9		12				
Diet	Day	Normal Blood, Mg.	2 Blood, Mg.	4 Blood, Mg.	Blood, Mg.	Plasma, Mg.	Blood, Mg.	Plasma, Mg.	13 Plasma, Mg.	14* Plasma, Mg.	20 Blood, Mg.
						Mg. per 100 Cc.					
Food....	1	..	..	..	..	..	92	87	..	78	74
	2	78	92	99	98	..	95	87	93	77	84
Fast.....	1	102	..	85	98	88	103	84	88	..	80
	2	..	..	68	92	83	77	68	68	78	..
	3	..	85	69	77	69	59	54	65	52	..
	4	68	88	70	80	70	59	56	59	49	45
	5	..	77	69	77	64	55	53	68	51	44
	6	..	77	83	70	65	61	55	69	54	..
	7	78	68	72	73	67	60	54	74	59	53
	8	..	..	73	72	66	59	61	76	..	53
	9	80	..	82	81	79	69	67	72	..	55
	10	..	..	73	75	72	73	65	72	..	53
	11	..	66	68	75	71	79	68	64	..	58
	12	81	67	75	78	78	83	80	69	..	..
	13	..	..	96	75	72	86	82	75	..	..
	14	..	63	74	..	..	..	..	78	..	..
	15	77	..	84	..	..	..	..	..	..	..
	16	..	..	69	..	..	..	..	..	..	..
Food....	1	91	93	79	86	95	90	84	88	..	58†
	2	103	86	84	..	..	89	84	91	..	59
	3	..	80	99	87	83	82	78	85	..	59
	4	..	..	102	97	88	73	66	92	..	56
	5	..	..	110	..	..	83	76	..	..	54
	6	..	..	99	..	..	70	..	..	..	59
	7	..	..	100	..	..	81	..	..	..	..

* Sugar measurements for this period made by the method of Benedict.[28]
† High fat diet.

ran a roughly parallel course. During fasting, concentration of sugar in the blood could be increased by injection of epinephrine. Concentration of glucose in plasma was constantly lower than in whole blood. In the latter, glucose did not fall below 55 mg. per hundred cubic centimeters, except in the case of the youngest member of the group, a girl of 13 years (subject 20), in whom the blood sugar fell to 44 mg.

14. Haden, R. L., and Orr, T. G.: J. Exper. Med. **37**:365 (March) 1923.
15. Hoeffel, G., and Moriarty, M.: Am. J. Dis. Child. **28**:16 (July) 1924.
16. Harding, V. J.; Allin, K. D.; Eagles, B. A., and Van Wyck, H. B.: J. Biol. Chem. **63**:37 (Feb.) 1925.

Evidently the condition in children differs from that in adults. During five fasting periods in children, Shaw and Moriarty [17] encountered a very low level of blood sugar. The average minimum amount in their children was 46 mg., whereas in our adults it was 65 mg.

Weeks and associates [18] made weekly measurements of blood sugar in seventy-three epileptic patients fasted for three weeks. These patients and the dogs of Morgulis and Edwards [13] showed, after an initial drop, increasing concentrations of sugar in the blood as the fasts progressed.

CHOLESTEROL

Table 6 gives the results of measurements of cholesterol during the fast of three patients. (The observations in this table are not controlled by data from healthy subjects.) The results are conflicting. The first

TABLE 6.—*Measurements of Cholesterol During Fasting*

		Mg. per 100 Cc. of Plasma		
Diet	Day	Subject 15	Subject 8	Subject 16 (Serum)
Food	1	...	190	...
Fast	1	91	...	...
	2	93	...	...
	4	...	143	159
	5	...	...	101
	6	118	...	...
	7	...	140	...
	8	132	...	...
	9	154	...	...
	10	156	152	...
	11	174	...	...
Food	1	...	...	190
	4	...	186	...
	7	...	...	286

patient 15 had a very low concentration of cholesterol in the blood at the beginning of the fast. The amount increased steadily during eleven days of fast. The patient died shortly after so that postfasting readings were not secured. With two other patients cholesterol was much lower during fasting than before or after. These conflicting observations are similar to results obtained with animals.

Bloor [19] found that blood fat increased during the first four or five days of fasting in three dogs and remained constant in three. One of the latter, when stuffed with fat and starved again, showed increase of fat in the blood. Greene and Summers [20] found that blood fat increased

17. Shaw, E. B., and Moriarty, M.: Hypoglycemia and Acidosis in Fasting Children with Idiopathic Epilepsy, Am. J. Dis. Child. **28**:553 (Nov.) 1924.

18. Weeks, D. F.; Renner, D. S.; Allen F. M., and Wishart, M. B.: J. Metabolic Res. **3**:201 (Feb.) 1923.

19. Bloor, W. R.: J. Biol. Chem. **19**:1, 1914.

20. Greene, C. W., and Summers, W. S.: Am. J. Physiol. **40**:146 (March) 1916.

in fasting puppies and remained constant in fasting dogs. With regard to cholesterol, Terroine [21] reported a progressive decrease during the prolonged fasting of dogs. Rothschild,[22] on the contrary, found an increase in four rabbits fasted from two to nine days.

TOTAL CALCIUM AND INORGANIC PHOSPHORUS

Gamble, Ross and Tisdall [23] found no change in plasma calcium at the end of four days of fasting in a child. Bigwood [24] found increase but his measurements were calculated values for ionized calcium. We have seen no observations concerning the behavior of blood phosphorus

TABLE 7.—*Measurements of Inorganic Phosphorus and Calcium During Fasting*

		Phosphorus, Mg. per 100 Cc. of Plasma					Calcium, Mg. per 100 Cc. of Plasma				
Diet	Day	Subject 11 (Normal)	Subject 15	Subject 8	Subject 17 (Serum)	Subject 16 (Serum)	Subject 11 (Normal)	Subject 15	Subject 8	Subject 17 (Serum)	Subject 16 (Serum)
Food.....	1	...	...	3.53	....	....	....	....	11.6	....	....
	2	...	...	3.13	3.3	....	....	....	10.3	....	....
Fast.....	1	5.0	...	....	3.25	....	12.3	....	....	....	....
	2	3.5	2.8	....	....	....	15.0	12.6	....	12.6	....
	3	3.1	2.6	....	....	....	14.6	11.5	....	11.4	....
	4	2.4	2.4	2.50	....	2.91	12.5	14.1	10.6	....	....
	5	...	...	....	2.78	....	....	....	....	....	12.0
	6	...	...	....	....	....	....	....	....	....	11.9
	7	...	...	2.50	....	....	....	....	9.1	....	....
	8	...	...	....	2.25	2.86	....	....	....	12.3	....
	9	...	...	4.17) 2.86\	....	....	....	....	13.8) 17.4\	....	....
	10	...	2.6)	4.17	....	....	....	10.0)	13.8	....	...
			2.9\					11.4\			
	11	...	3.0	2.2?	....	2.50	....	12.0	15.5	....	11.3
	12	...	2.5	....	3.33	....	....	11.8	....	11.6	....
	13	...	...	....	....	....	....	....	9.9	....	....
	14	...	2.0	....	....	....	....	12.9	....	....	....
Food.....	1	...	2.4	....	....	3.33	....	13.9	....	....	9.3
	2	...	...	....	....	....	....	....	....	....	....
	3	...	2.6	....	....	....	....	12.1	....	....	....
	4	...	3.0	2.50	....	....	....	....	10.5	....	....
	5	...	...	2.50	2.30	....	....	....	....	11.1	....
	6	...	...	....	2.63	....	....	....	....	14.1	....
	7	...	...	3.60	....	2.50	....	....	....	....	10.2

in fasting. The four epileptic subjects whose calcium and phosphorus we measured during fasting (table 7) showed no significant variations from their normal levels, except that one patient who was given 30 Gm. of calcium chloride by mouth showed subsequent increase in the calcium of his plasma. The normal control who fasted four days showed increase in blood calcium and coincident decrease in phosphorus during a four day fast. The period was unsatisfactory, however, because, for other purposes, fasting was preceded by the ingestion of 79 grains (5 Gm.) of thyroid extract.

21. Terroine, E. F.: J. de physiol. et de path. gen. **16**:386, 1914.
22. Rothschild, M. A.: Beitr. z. path. anat. **60**:227, 1915.
23. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: J. Biol. Chem. **57**:633 (Oct.) 1923.
24. Bigwood, E. J.: Compt. rend. Soc. de biol. **90**:98 (Jan. 25) 1924.

TABLE 8.—*Measurements of Blood Fibrin During Fasting*

		Mg. per 100 Cc.					
		Plasma			Whole Blood		
Diet	Day	Subject 4	Subject 12	Subject 13	Subject 4	Subject 12	Subject 13
Food	1	...	...	418	...	...	246
	2	...	...	416	...	...	239
Fast	1	373	...	...	184	...	...
	2	336	300	...	166	169	...
	4	301	...	...	130	...	...
	5	305	345	...	137	192	...
	6	385	...	...	168	...	...
	8	...	351	...	...	206	...
	10	355	...	364	150	...	224
	11	...	323	...	...	189	...
	13	297	...	...	159	...	...
	14	...	323	...	...	192	...
	15	272	...	...	147	...	...
Food	2	314	...	...	152	...	...
	4	291	...	345	154	...	208
	7	303	...	...	164	...	...
	10	359	332	...	170	207	...
	11	374	...	...	191	...	...
	21	382	...	...	213	...	...

TABLE 9.—*Measurements of Plasma Bicarbonate During Fasting*

		Subjects									
		11	5	1	18	7	19	8	4	9	13	14
		Per Cent by Volume Carbon Dioxide										
Diet	Day	Normal		(second)								
Food	1	....	....	....	68.0	....	61.2	68.5	....	....	66.8	....
	2	70.0	....	....	65.3	66.3	58.2	70.4	....	....	65.0	75.3
Fast	1	69.7	60.3	60.7	63.8	64.2	60.2	69.8	56.6	61.0	64.5	73.8
	2	62.2	....	....	59.0	57.4	62.3	69.0	53.7	49.3	54.1	71.4
	3	48.6	59.3	....	55.2	50.1	53.7	65.5	43.9	....	44.7	51.8
	4	40.5	54.0	47.0	....	....	56.4	61.4	47.6	55.3	37.9	49.8
	5	33.2	40.5	52.5	55.9	55.7	47.0	60.7	48.5	54.2	36.5	49.1
	6	36.4	43.2	....	60.2	55.3	....	59.7	....	52.4	39.4§	46.1
	7	45.1	37.2	49.0	58.5	53.4	50.0	57.0	46.5	54.8	43.7	47.7
	8	44.7	40.4	....	60.7	55.6	51.2	61.1	48.0	48.1	44.6	....
	9	52.1	44.5	....	59.5	55.1	55.5*	44.4†	45.9	50.3	45.6	....
	10	49.6	....	....	....	59.2	53.0	51.7	44.9	57.7	41.1	....
	11	54.0	48.3	....	59.8	56.5	51.3	61.0	....	57.5	44.6	....
	12	54.0	....	53.2	57.2	63.2	....	87.0‡	44.5	63.3	47.2	....
	13	52.3	49.5	....	59.3	55.5	....	77.8	48.0	63.0	45.5	....
	14	51.0	49.4	....	63.0	52.5	60.8	74.0	76.6	....	40.2	....
	15	49.3	45.7	....	59.0	....	67.3	65.3	66.4	....	....	....
	17	....	....	53.3	57.4	....	60.3	63.5	....	....	....	....
	19	....	....	58.2	....	....	....	....	....	....	....	....
	21	....	....	55.0	....	....	....	....	....	....	....	....
Food	1	66.0	59.5	....	68.3	....	64.7	....	....	76.5	49.6	....
	2	72.5	....	68.5	69.0	....	69.5	71.4	....	....	63.9	....
	3	73.2	71.0	....	73.0	....	....	74.5	....	77.0	63.6	....
	4	72.5	68.5	....	68.5	....	65.0	69.5	....	66.0	64.2	....
	5	74.4	63.5	....	68.8	....	67.2	68.6	....	....	65.4	....
	6	77.8	....	....	....	....	66.0	....	....	....	71.6	....
	7	75.0	65.0	....	....	....	65.3	....	....	....	....	....
	8	68.2	....	....	....	....	....	....	....	....	....	....
	9	66.3	....	....	....	....	....	....	....	....	....	....
	10	67.5	....	....	....	....	....	....	....	....	....	....

* Fifty-four grains (3.5 Gm.) thyroid extract taken during subsequent five days.
† Thirty-five grams of calcium chloride taken during following forty-eight hours.
‡ An alkaline mixture taken during following forty-eight hours.
§ Severe vomiting; given 50 Gm. of glucose.

FIBRIN

We have seen no observations concerning the behavior of blood fibrin during fasting. In the three fasts of patients detailed in table 8 it will be seen that there was considerable fluctuation in values from day to day. Measurements during fasting tended to be lower in two cases and slightly higher in one.

PLASMA BICARBONATE

That reduction in the bicarbonate of the plasma attends the ketosis of fasting is well known. This has been demonstrated in rabbits by Asada [25] and in human subjects by Koehler,[26] Gamble, Ross and Tisdale,[23] Shaw and Moriarity,[17] Bigwood [27] and others.[28] Table 9

TABLE 10.—*Titratable Acidity of Urine and Excretion of Ammonia During Fourteen Days' Fast of Healthy Subject 11*

Diet	Day	Titratable Acidity			Ammonia			p_H	
		Night	Day	24 Hours	Night	Day	24 Hours	Night	Day
Fast	1	230	...	...	0.34	0.13	0.47	5.3	5.9
	2	280	271	551	0.26	0.38	0.66	5.5	5.4
	3	241	369	610	0.60	0.84	1.44	5.4	5.3
	4	420	396	816	1.32	1.23	2.55	5.3	5.4
	5	385	345	730	1.25	1.38	2.63	5.4	5.7
	6	257	216	473	1.20	1.36	2.56	5.9	6.0
	7	167	157	324	1.28	1.24	2.52	6.0	6.0
	8	...	182	...	1.17	1.31	2.48	5.9	5.8
	9	122	153	275	0.80	1.27	2.06	6.0	6.3
	10	152	167	319	1.14	1.21	2.35	6.3	6.1
	11	187	169	356	1.34	1.06	2.40	6.0	6.1
	12	154	148	302	1.06	1.27	2.33	6.1	6.2
	13	113	133	246	0.85	0.92	1.77	6.2	6.1
	14	141	136	277	0.99	0.97	1.96	6.1	6.1
Fat	1	131	112	243	0.84	0.94	1.78	6.0	6.4
Low fat	1	74	52	126	0.40	0.14	0.55	6.6	6.5
Protein	2	41	40	81	0.15	0.16	0.31	6.4	6.2
	3	43	...	...	0.15	....	....	6.2	5.9

presents daily measurements of plasma bicarbonate (carbon dioxide combining power of the plasma) in normal subject 11 and seven patients. Inspection of the table shows the following:

In every case there was reduction of plasma bicarbonate but the amount varied in different subjects. The greatest reduction occurred from the third to the seventh days of fast. After the first week the acidosis gradually diminished, and plasma bicarbonate tended to approach the prefasting values. Following the ingestion of food, there was an increase of bicarbonate to above the prefasting level, a mild degree of alkalosis.

Two measurements of p_H of the blood were made during two fasts of normal subject 11. On the fifth day of the first fast when plasma

25. Asada, H.: Am. J. Physiol. **50**:1 (Oct.) 1919.
26. Koehler, A. E.: Acid-Base Equilibrium: Clinical Studies in Alkalosis, Arch. Int. Med. **31**:590 (April) 1923.
27. Bigwood, E. J.: Ann. de méd. **15**:119 (Feb.) 1924.
28. Benedict, S. R.: J. Biol. Chem. **64**:207 (May) 1925.

bicarbonate was 33 per cent by volume, p_H of the blood was 7.2 (measured by Dr. Bock by means of carbon dioxide dissociation curve). On the third day of a fourth fast, the p_H of the blood was 7.37 (measured by Dr. Koehler by gas chain method). In this subject, therefore, the depletion of bicarbonate of the blood resulted in an uncompensated acidosis. It will be noticed that the patients showed a smaller reduction of bicarbonate than the normal subject. Whether this is due to the fact that they were less active during the fast or to some inherent tendency against development of acidosis in epilepsy is not yet clear.

ACID EXCRETION

As a corollary to the observations concerning the plasma bicarbonate of normal subject 11, table 10 presents data concerning acid and ammonia excretion. It will be observed that titratable acidity was greatest during

TABLE 11.—*Concentration of Various Constituents During a Short Fast Without Water of Normal Subject 11*

	Day	Water Intake, Cc.	Mg. per 100 Cc. of Plasma: Nonprotein Nitrogen	Uric Acid	Sugar	Fibrin	Bicarbonate per Cent by Volume Carbon Dioxide	Hemoglobin (Sahli)
Prefasting.....	1	3,550	..	3.2	90	358	73.8	81.2
	2	1,800	..	3.4	95	...	68.6	....
Fast.....	1	None	..	3.4	90	...	70.7	....
			22	3.4	..	....	....	....
			23	4.8	76	...	62.3	....
	2	None	30	4.7	68	...	54.8	....
			33	5.6	..	....	....	....
			26	6.2	71	374	73.8	94.5
	3	None	33	6.2	62	...	52.0	....
			35	7.1	..	...	54.9	104
			29	7.7	68	420	52.5	104
	4	2,500	31	8.6	70	...	48.0	....
			30	9.3	..	...	47.2	101
Postfasting*.....	1	1,800	21	8.9	75	...	50.2	....
			18	8.3	..	....	57.7	....
	2	2,400	26	4.2	99	354	57.7	....
	3	.....	23	3.4	104	...	68.5	....

* A three day interval between this and preceding observation.

the period when depletion of bicarbonate was greatest. With the increase in titratable acidity, there was increased excretion of ammonia, so that after the first few days the p_H of the urine remained practically normal.

FASTING WITHOUT WATER

In a six day fast of healthy subject 11, no water was taken during the first seventy-five hours (table 11). During this period, plasma bicarbonate did not fall nor uric acid rise so fast as in previous fasts in which water was drunk. This was presumably due to the unusually rapid destruction of body protein, as evidenced by increased basal metabolism, rapid loss of body weight, and marked fluctuation in the concen-

tration of nonprotein nitrogen in the plasma (comparison should be made with table 3). The question of protein metabolism in fasting will be discussed in more detail elsewhere. The increase of fibrin during the period without water could be accounted for largely by anhydremia, for there was coincident increase in hemoglobin from 81 to 104 per cent.

SUMMARY

Observations of chemical changes in the blood made during and subsequent to thirty fasting periods of epileptic and normal subjects showed the following:

During fast nonprotein and urea nitrogen varied considerably from day to day, with a tendency toward increased concentration; amino-acid nitrogen remained remarkably constant and uric acid rose independently of other constituents examined. In the period of refeeding, nonprotein and urea nitrogen and uric acid fell to subnormal levels.

Sugar fell to a low level during the first week, rising again as the fast progressed. Concentration in plasma was constantly lower than in whole blood.

Inorganic phosphorus and calcium remained constant, and cholesterol and fibrin showed both increase and decrease (three patients).

Plasma bicarbonate was greatly reduced, coincident with increase in total acid excretion.

In a three day fast without water, there was evidence of unusual increase in protein metabolism.

THE OUTPUT OF THE HEART PER BEAT IN HYPERTHYROIDISM *

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AND
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In a previous article [1] the measurement of the output of the heart per beat, by direct determination of the oxygen contents of arterial and venous blood, was shown to be a practical clinical procedure. Marked and consistent differences were noted between the values obtained in normal persons and in those with heart failure. The results in normal subjects agreed very closely with those obtained by other methods employed by physiologists and regarded as reliable. Briefly the test consists of the simultaneous determination of (*a*) the oxygen contents of arterial and venous bloods; (b) the oxygen requirement of the tissue per minute, and (*c*) the pulse rate. From these are calculated in order (*a*) the oxygen consumption, that is, the difference between the arterial and venous oxygen contents; (*b*) the total output of blood per minute from the heart, and (*c*) the output per beat. Thus, $T = \frac{100 \times R}{P\ (A - V)}$, in which

T = output per beat (cubic centimeters)

R = oxygen requirement (cubic centimeters per minute)

A = arterial oxygen content (cubic centimeters per hundred cubic centimeters)

V = venous oxygen content (cubic centimeters per hundred cubic centimeters)

P = pulse rate

The most probable objection which may be made to this procedure is to the assumption that values of the oxygen content of venous blood taken from arm veins are the same as in the blood in the right heart. It is generally recognized that variations in the oxygen content of blood from an arm vein may be caused by conditions other than the volume output of the heart. Of special note are temperature of the environment and muscular activity. This objection may be met with in at least two ways. It was shown (1) that in normal persons *under the constant set of conditions described* the variations in the oxygen unsaturation of venous blood in this region were remarkably constant and small. Numerous analyses made since have given the same results. The wide

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* From the Department of Metabolism, Montreal General Hospital.

1. Rabinowitch, I. M.: The Output of the Heart Per Beat in Heart Disease, Arch. Int. Med. **36**:239 (Aug.) 1925.

fluctuations recorded by different authors have been met with only occasionally. The comparative data are shown in table 1. These observations alone suggest the reliability of this procedure. The important fact, however, is that the results obtained in normal persons agree with those obtained by other methods of determining circulation rates and regarded as reliable. This has recently received confirmation as the following observations demonstrate.

Field, Bock, Gildea and Lathrop [2] recently determined circulation rates in normal resting subjects. Their method involved simultaneous determinations of alveolar and venous carbon dioxide tensions. From some of their data it was possible to compare the results of both methods. These authors recorded in each case the oxygen capacity of the blood, the oxygen saturation of venous blood and the rate of carbon dioxide

TABLE 1.—*Variations in Oxygen Unsaturation of Venous Bloods*

	Venous Oxygen Unsaturation	
	Cc.	Average
10 normal persons (authors' cases) published	3.5 to 5.5	4.2
42 normal persons (authors' cases) unpublished	3.0 to 5.2	4.4
55 persons with anemia (Lundsgaard)	2.5 to 5.5	
40 determinations on 4 subjects with compensated heart lesions (Lundsgaard)	1.5 to 5.6	
15 normal persons (Harrop)	2.6 to 8.8	
12 normal persons (Lundsgaard)	2.5 to 9.0	
12 patients with compensated heart lesions (Lundsgaard)	2.5 to 8.0	

elimination. From the data representing the oxygen capacity and the oxygen saturation of the venous bloods, one may calculate their oxygen contents. If the arterial bloods are assumed to be 95.4 per cent saturated with oxygen, and the average respiratory quotient in the postabsorptive state is accepted as 0.82, it is then possible to obtain, respectively, values for the oxygen contents of the arterial bloods and oxygen consumptions by the tissues per minute. From these data one may then calculate the circulation rates as above and compare them with those actually found. Thus:

Subject F. W. L. (Field, Bock, Gildea and Lathrop)

Oxygen capacity = 20.0

$\therefore$ arterial oxygen content = $0.954 \times 20.0 = 19.1$ cc.

Oxygen saturation of venous blood = 77 per cent.

$\therefore$ Venous oxygen content = $20.0 \times 0.77 = 15.4$.

$\therefore$ Oxygen consumption = $(19.1 - 15.4) = 3.7$.

Carbon dioxide elimination per minute = 204 cc.

Respiratory quotient = $0.82 = \frac{204}{x}$ where x = oxygen consumption per minute by tissues

2. Field, H.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, J. Clin. Investigation **1**:65, 1924.

$\therefore$ Oxygen consumption per minute $= 248.7$ cc.

$\therefore$ Circulation rate per minute $= \frac{248.7 \times 100}{3.7} = 6.72$ liters.

The value actually found by Field, Bock, Gildea and Lathrop in this case was 7.03 liters.

All the rates recorded by Field, Bock, Gildea and Lathrop were recalculated as above. The combined data are recorded in table 2. In order are recorded (*a*) the oxygen capacity; (*b*) calculated arterial oxygen contents; (*c*) percentage venous oxygen saturation; (*d*) calculated venous oxygen contents; (*e*) oxygen consumption; (*f*) carbon dioxide elimination rates; (*g*) calculated oxygen requirements; (*h*) calculated circulation rates, and (*i*) actual circulation rates (liters per minute). The results are striking as the following average values show.

Actual circulation rate (Bock et al.) $= 7.97$ liters per minute.

TABLE 2.—*Actual (Bock et Al.) and Calculated (Authors' Method) Circulation Rates*

Subject	Oxygen Capacity	Calculated Arterial Oxygen Content (s) × 0.954	Percentage Saturation Venous Blood	Calculated Venous Oxygen Content (a) × (c)	Oxygen Consumption (b) — (d)	Carbon Dioxide Elimination, Cc. per Minute	Calculated Oxygen Requirement, Cc. per Minute 0.82 × (f)	Calculated Circulation Rate, Liters per Minute	Actual Circulation Rate, Liters per Minute
F. W. L.	20.0	19.1	77.0	15.4	3.7	204.0	248.7	6.72	7.03
F. W. L.	19.9	19.0	76.6	15.2	3.8	204.0	248.7	6.54	6.69
F. T. H.	18.2	17.4	74.0	13.5	3.9	139.3	170.0	4.36	4.50
C. M. J.	21.5	20.5	83.0	17.8	2.7	171.5	209.1	7.74	7.80
C. M. J.	20.3	19.4	83.2	16.9	2.5	155.0	189.0	7.16	7.64
J. M. F.	18.0	17.2	77.2	13.9	3.3	201.7	246.0	7.48	7.47
A. V. B.	20.0	19.1	70.8	14.2	4.9	190.3	232.1	4.74	4.76
A. V. B.	21.6	20.6	75.0	16.2	4.4	174.2	212.4	4.80	4.84
H. F.	20.1	19.2	85.4	17.2	2.0	200.0	243.9	12.20	12.90
H. F.	20.8	19.8	83.6	17.4	2.4	208.0	253.6	10.60	10.40
H. F.	19.6	18.7	84.8	16.7	2.0	200.0	243.9	12.20	11.70
H. F.	22.1	21.1	82.6	18.3	2.8	193.8	236.3	8.40	8.40
H. F.	21.0	20.0	84.3	17.7	2.3	213.0	259.7	11.30	11.20
S. L. W.	22.6	21.6	74.0	16.7	4.4	214.0	261.0	6.04	5.30
H. P. S.	21.7	20.7	82.1	17.8	2.9	212.0	258.5	8.91	9.00
Average								7.94	7.97

Calculated circulation rate (authors') $= 7.94$ liters per minute.

Subsequently observations to be discussed presently further demonstrated the reliability of this procedure.

During a study [3] made in testing the theory of ammonia formation by the kidneys, it was found necessary to obtain data relative to circulation rates. The subjects were carefully selected for this purpose. They were all severe diabetes patients with marked acidosis. That they were ideal subjects to test the clinical value of this method of determining circulation rates will be observed from the following considerations.

A bright red color of the skin is frequently associated with the severe acidosis of diabetes. This color is usually accompanied by a

3. Rabinowitch, I. M., and Bazin, Eleanor V.: Ammonia Formation by the Kidneys, to be published.

TABLE 3.—*Circulation Rates of Severe Diabetic Patients with Acidosis and Increased Basal Metabolic Rates*

No.	Total Organic Acids, Cc. Tenth Normal per 24 Hours	Plasma Carbon Dioxide, per Cent by Volume	Height, Cm.	Weight, Kg.	Body Surface, Square Meters	Age	Sex*	Basal Metabolic Rate	Oxygen Capacity, Cc. per 100 Cc.	Oxygen Content Arterial Blood (A)	Oxygen Saturation Arterial Blood, per Cent	Oxygen Content Venous Blood (V)	Oxygen Unsaturation Venous Blood, Cc.	A — V	Oxygen Intake, Cc per Minute	Cardiac Output, Liters per Minute	Pulse	Cardiac Output per Beat	Cardiac Output per Beat, Cc. per Kg. Body Weight
1	5,750	31.7	170.7	50.1	1.58	32	♂	+24.6	18.7	18.4	98.4	14.6	4.1	3.8	269	7.078	82	86.3	1.72
2	4,175	26.1	165.4	53.8	1.59	36	♂	+23.0	17.6	17.4	98.8	13.7	3.9	3.7	267	7.216	92	78.3	1.45
3	4,680	34.7	163.1	59.7	1.64	26	♂	+20.0	19.0	18.8	98.9	15.3	3.7	3.5	305	8.714	108	80.7	1.35
4	4,130	28.1	167.4	55.1	1.61	46	♀	+26.3	15.9	16.7	98.8	13.9	3.0	2.8	253	9.034	86	105.0	1.90
5	3,175	35.7	170.8	54.6	1.63	41	♀	+25.2	19.4	19.2	98.9	16.7	2.7	2.5	254	10.160	94	108.0	1.97
6	4,520	34.9	165.9	72.0	1.80	57	♂	+24.8	18.3	18.1	98.8	15.0	3.3	3.1	291	9.387	92	102.0	1.40
7	2,764	38.4	178.2	68.1	1.85	34	♂	+20.4	20.3	20.0	98.5	17.8	2.5	2.2	304	13.818	110	125.6	1.84
8	3,964	33.0	162.6	70.1	1.76	29	♀	+19.5	17.6	17.1	97.1	15.0	2.6	2.1	269	12.809	98	137.2	1.95
9	4,116	31.2	173.1	65.4	1.78	36	♂	+21.6	16.9	16.6	98.2	13.7	3.2	2.9	294	10.139	114	89.0	1.36
10	3,446	41.7	165.4	63.2	1.69	42	♂	+22.3	15.5	15.3	99.0	11.9	3.6	3.4	275	8.089	78	103.7	1.64
11	5,474	29.8	160.3	62.4	1.65	39	♂	+16.7	16.6	16.4	98.7	13.9	2.7	2.5	263	10.520	96	109.6	1.75
12	3,119	36.7	170.2	64.1	1.74	41	♂	+18.4	19.6	19.1	97.4	15.5	4.1	3.6	274	7.611	79	96.3	1.50
Average								22	....	....	98.4	....	3.2	3.0	...	9.548	94	121.7	1.67

* In this column, ♂ indicates male; ♀, female.

low oxygen unsaturation of venous blood. The basal metabolic rate also is usually increased in this state. These two conditions being present at the same time it is obvious that the increased oxygen intake must be accompanied by an increase in the circulation rate. It is now therefore necessary to note whether, given these two sets of conditions, an increased circulation rate is found by this method. In table 3 are recorded the data demonstrating this phenomenon.

The cases appear to be of the severe type. All patients exhibited a "good" color and the Küssmaul type of respiration. The severity in each case may be judged from the laboratory data recorded in the table; namely, (*a*) the excretion of large quantities of organic acids and ammonia in the urine; (*b*) the low carbon dioxide combining power of the plasma; (*c*) the state of undernutrition, judging from the weight-height-age relationships, and (*d*) increased metabolic rates. In no case was there any suggestion of heart failure except for the tachycardia. In each case it will be noted that the circulation rate was increased. This appears to give further proof of the reliability of this procedure. In table 4 are briefly summarized the results, and these are compared with the normal.

TABLE 4.—*Maximum, Minimum and Average Cardiac Outputs in Normal Persons and in Diabetic Patients with Acidosis*

Subjects	Average	Maximum	Minimum
Normal	6304.0	7531.0	5052.0
Diabetic	9548.0	13818.0	7078.0

Because of these findings, this method was employed in a series of cases of hyperthyroidism. For comparative purposes hyperthyroid subjects were chosen whose basal metabolic rates, with few exceptions, approximated those found in the series of diabetic cases studied. The basal metabolic rates in fifteen of the twenty cases ranged between plus 15 and plus 36 per cent. All cases belonged to the exophthalmic goiter or toxic hyperplastic group. In no case was there evidence suggestive of heart failure other than tachycardia.

The procedure in this study was simplified by making no actual observations on arterial blood. This appeared justifiable. In the absence of pulmonary congestion or heart lesions suggesting the presence of the latter (mitral stenosis) or congenital anatomic defects, it may reasonably be assumed, as shown by numerous workers, that the arterial blood is fairly completely saturated with oxygen. In ten normal subjects we found that the average saturation of the arterial blood was 95.4 per cent; this agrees very closely with the results of other workers. (Higher values were found in the diabetic series.) The combined data are recorded in table 5.

TABLE 5.—*Circulation Rates in Hyperthyroidism*

Number	Height, Cm.	Weight, Kg.	Body Surface, Square Meters	Age	Sex*	Basal Metabolic Rate, per Cent Above Normal	Oxygen Capacity, Cc. per 100 Cc.	Oxygen Content Arterial Blood (A)	Oxygen Content Venous Blood (V)	Oxygen Unsaturation Venous Blood, Cc.	A — V	Oxygen Intake, Cc. per Minute	Cardiac Output, Cc. per Minute	Pulse	Cardiac Output, Cc. per Beat	Cardiac Output per Beat, Cc. per Kg. Body Weight
1	160.0	49.1	1.49	70	♂	31	16.5	15.7†	9.5	7.0	6.2	240	3,871	106	36.5	0.74
2	163.0	45.3	1.46	47	♀	37	15.7	15.0	11.4	4.3	3.6	250	6,944	112	62.0	1.36
3	171.0	66.8	1.78	17	♂	19	17.2	16.4	10.7	5.7	6.5	290	5,087	108	47.1	0.701
4	169.6	61.9	1.72	55	♂	40	14.9	14.2	9.8	3.4	5.1	316	7,182	136	52.8	0.85
5	163.3	45.3	1.46	26	♀	52	16.1	15.3	11.2	3.1	4.9	290	7,073	109	64.9	1.43
6	158.6	46.8	1.45	47	♀	34	16.2	15.4	11.6	3.8	4.6	243	6,395	104	61.5	1.31
7	154.8	66.1	1.65	25	♀	32	14.8	14.1	9.8	4.3	5.0	280	6,512	118	55.1	0.83
8	165.1	52.3	1.56	58	♂	55	16.5	15.7	11.3	4.4	5.2	315	7,159	110	65.1	1.24
9	153.4	69.7	1.68	64	♀	26	18.0	17.2	14.0	3.2	4.0	250	7,812	114	68.5	0.98
10	175.2	67.4	1.81	40	♂	36	13.9	13.2	9.1	4.8	4.1	328	8,000	116	68.9	1.02
11	155.0	55.8	1.54	37	♂	16	15.8	15.1	11.5	4.3	3.6	245	6,805	114	59.6	1.07
12	164.8	53.9	1.59	23	♂	24	15.9	15.2	11.5	4.4	3.7	270	7,297	100	73.0	1.35
13	157.7	52.1	1.51	20	♀	36	17.3	16.5	11.1	6.2	5.4	264	4,889	112	43.6	0.83
14	175.1	52.7	1.64	63	♂	32	16.4	15.6	10.7	5.7	4.9	275	5,612	120	46.7	0.88
15	155.1	43.9	1.39	25	♀	41	15.8	15.1	12.0	3.8	3.1	253	8,161	117	69.8	1.59
16	162.8	44.4	1.44	22	♂	22	14.9	14.2	10.5	4.4	3.7	241	6,513	109	59.7	1.34
17	164.7	74.4	1.81	24	♂	12	15.6	14.9	9.1	6.5	5.8	279	4,810	113	42.6	0.57
18	163.4	46.8	1.48	26	♀	49	16.4	15.6	9.5	6.9	6.1	282	4,623	124	37.3	0.80
19	168.2	54.2	1.61	23	♂	32	17.1	16.3	9.5	7.6	6.8	292	4,294	118	36.4	0.67
20	155.3	55.6	1.54	37	♂	24	16.9	15.2	10.9	5.1	4.3	262	6.093	110	55.4	0.99
Average																1.02

* In this column, ♂ indicates male; ♀, female.
† Arterial blood assumed to be 95.4 per cent saturated.

RESULTS

It will be noted that in each case in this series, with one exception, the volume output of the heart per beat was diminished. As just stated, in no case was there any other evidence suggestive of heart failure, with the exception of the tachycardia. The average output per beat was 55.3. The maximum and minimum values were 73 and 36.4, respectively. It would therefore appear that all these patients had some heart failure. A comparative study of the pulse rate, metabolic rate ratios and cardiac outputs per kilogram of body weight in the diabetic and hyperthyroid cases tends to corroborate this finding. For comparative purposes only those cases of hyperthyroidism with metabolic rates not greater than the maximum found in the diabetic cases are now considered. Table 6 shows the relation between the average pulse rate and average metabolic rate.

TABLE 6.—*Relation Between Average Pulse and Average Metabolic Rates*

	Hyperthyroidism	Diabetes With Acidosis
Average pulse rate per minute	110	94
Average metabolic rate (increase above normal, per cent)	20	22

Since the average basal metabolic rates in both series of cases were approximately the same, it appears reasonable to assume that some factor other than increased metabolism must account for the excess increase in pulse rate in the cases of hyperthyroidism. The pulse rate = metabolic rate ratio incidentally offers further evidence, if necessary, of the value of the pulse rate in determining the presence of heart failure.

Further evidence of heart failure in these cases of hyperthyroidism is found in a comparative study of the circulation rates of the normal, diabetic and hyperthyroid subjects. Table 4 shows the influence of work (increased basal metabolic rate) on circulation rate. In the cases of diabetes with acidosis with an average increase of 22 per cent in the basal metabolic rate and no heart failure the average volume output of blood per minute increased about 50 per cent. In the cases of hyperthyroidism with a corresponding increase in basal metabolic rate the average volume output per minute approached only that found in the normal resting person. The average volume output per minute was 6.345 liters. It will also be noted (tables 3 and 5) that, unlike in the cases of diabetes, the majority of the circulation rates noted in hyperthyroidism have fallen below Henderson's[4] estimate of the normal cardiac output; namely, 1.5 to 2.0 cc. per kilogram of body weight per beat. In the absence of other clinical evidence of heart failure, the clinical value of such a study as the foregoing is obvious.

4. Henderson, Y.: Physiological Rev. **3**:165 (April) 1923.

ROENTGEN-RAY THERAPY IN ERYSIPELAS *

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There probably are few diseases known to man which have caused as much speculation regarding their treatment as erysipelas. Standard textbooks and current medical literature allude to many forms of therapy, among which are well known local applications such as sulphonated bitumen, N. F., zinc stearate, magnesium sulphate, alcohol glycerin, mercurochrome-220 soluble, phenol, lead water, mercuric chloride, picric acid and iodine in various combinations. In addition whole blood, serums, leukocytic extracts and vaccine have all been exploited. Recently Alquier [1] and others have advocated the use of ultraviolet radiation. The multiplicity and variability in methods of treatment in a given disease probably indicate an uncertainty as to the value of all of these therapeutic procedures and the lack of uniform success following their employment only stresses the fact that the disease in question is more or less self limited. Erysipelas stands out as a striking example of this group of diseases, a fact that is quite well accepted.

In view of these numerous and varied attempts in the treatment of erysipelas it is rather singular that so little attention has been paid to the use of roentgen rays, particularly since satisfactory results have been obtained by this procedure. Hesse [2] and Schrader [3] reported encouraging results by the method but had no control cases and used comparatively small repeated doses. Occasional isolated cases are mentioned [4] in the American literature in connection with groups of pyodermias that have been subjected to roentgen ray. Platou [5] and Rothneu [6] also have treated a number of cases of erysipelas and have been greatly impressed with the rapid improvement after exposure to the roentgen rays.

It is obvious that since erysipelas is a self limited disease any form of treatment to be adjudged effective must be so in a very prompt and definite manner. With this in mind we attempted to give the treatment

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1. Alquier, L.: Paris méd. **7**:145 (Aug. 18) 1917.
2. Hesse, W.: München. med. Wchnschr. **45**:505, 1918.
3. Schrader: Therap. Halbmonatsch. **35**:600, 1918.
4. Lawson, J. D.: Radiology **6**:153 (Feb.) 1926. Hodges, F. M.: Am. J. Roentgenol. **11**:442 (May) 1924.
5. Platou, L. S.: Personal communication to the author.
6. Rothneu: Personal communication to the author.

over as short a period and as soon as possible after the onset of the disease, hoping that such a procedure would eliminate to some extent the factor of natural improvement. It is apparent that the interpretation of results of a course of roentgen-ray treatments extending over a period of a week or two is always questionable whereas a sharp improvement occurring within one or two days after the administration of any therapy is much more convincing as to its efficacy. For this reason in our cases only one dose of roentgen rays was given and in most cases no other form of therapy was used thereafter except sedatives and analgesics. In the first few cases, our results were somewhat mediocre and it was soon apparent that a larger roentgen-ray dose would be necessary. The technic as finally evolved was as follows:

The facial cases were divided into four areas of exposure: one anterior, over the face and forehead; one on each lateral surface of the face and neck, including the ear, and one on the scalp. The first three areas were always treated regardless of whether they were all involved or not, in the hope of preventing a spreading of the disease to the normal areas. The area over the scalp was treated only when invasion or threatened invasion of it was in process. No protection was used except over the eyebrows. A distance of 10 inches from the tube to the skin of the patient was used over all the areas with 2 mm. of aluminum as a filter. The readings were 111 kilovolts (peak), corresponding approximately to a 7 inch spark gap between moderately blunt points, and 5 milliamperes for five minutes over each area. This was considered a dosage sufficient to produce a very mild erythema when the oblique radiation from each area was taken into account. Over the scalp the dosage was reduced to four minutes to avoid any possibility of producing permanent epilation. Only one treatment was given, all the areas being exposed on the one occasion. In the cases of erysipelas in other parts of the body the affected area, together with a large border of normal skin around it, was treated in the same way, the part to be treated being divided into contiguous areas of approximately 300 sq. cm.

Realizing that mere clinical impressions might lead to erroneous conclusions and that such impressions account for many of the avowed cures, we formulated comparative charts for the tabulating of important clinical data. Careful records were then kept of the patients who received roentgen-ray therapy and those who did not.

Briefly summarized reports of eighteen patients who were treated by iced magnesium sulphate and glycerin packs—the usual routine procedure—are given in table 1.

These eighteen patients were admitted to the hospital in the eight months just prior to the institution of the radiation therapy. They were taken in chronologic order and the only cases eliminated were those in which so many complicating factors were present before the onset of

TABLE 1.—*Data from Eighteen Patients with Erysipelas Treated by Iced Magnesium Sulphate and Glycerin Packs*

Case	Age	Duration at Time of Treatment, Days	Temperature	Extent of Infection	Degree of Infection	Time from Treatment to Normal Temperature, Days	Time to Normal Symptoms, Days	Extension After Treatment	Complications and Sequelae	Duration from Treatment to Cure, Days	Duration Whole Illness, Days
1	43	7	102.0	Face	Severe	..	..	Over neck	Death	..	..
2	60	3	104.0	Face only	Severe	5	5	Ears	Albuminuria	7	10
3	62	1	100.0	Forehead	Mild	3	5	No	None	5	6
4	64	4	103.4	Face, scalp	Severe	4	4	Left elbow	Albuminuria	7	14
5	60	7	98.0	Cheek, forehead	Mild	8	4	Ears	None	6	13
6	42	3	101.0	Ear, cheek	Mild	2	3	Over eye	None	4	4
7	32	7	104.0	Face, ear	Moderate	2	4	Right ear	None	5	12
8	65	6	102.4	Face, ears	Severe	9*	..	Back, arm	Gangrene, death	..	..
9	32	32	102.0	Face, neck	Moderate	7	8	Ears, arm, scalp	Tonsillitis	9	11
10	38	7	104.2	Face	Moderate	2	2	Ear	None	8	15
11	68	3	102.2	Face	Moderate	7	9	Ears	None	21	24
12	62	2	Nor.	Nose	Mild	..	3	No	None	5	7
13	70	2	101.0	Face, ear, scalp	Moderate	..	..	Neck, back, buttocks	Death	..	..
14	45	2	100.0	Nose, cheek	Mild	3	3	Ear	None	4	6
15	54	5	102.8	Forehead, cheek, ears	Moderate	11	12	Back, arms	None	17	22
16	22	3	103.8	Nose, cheek, forehead	Severe	4	5	Face	None	7	10
17	47	3	104.0	Face, elbow	Severe	..	..	Scalp, neck	Death	..	..
18	20	1	101.0	Cheek	Mild	8	8	Face, ear, neck	None	8	9

the erysipelas as to make it difficult to evaluate the results of the treatment. In table 2 are given similar reports of twenty-three cases, also unselected, which were treated with roentgen rays. The data in the two groups were selected on precisely the same basis. As the second group followed the first in chronologic order, both were studied in the contagious disease department of the Minneapolis General Hospital, and both were treated under the same conditions, and thus may be compared fairly well as to results.

The tables are self explanatory but certain important facts should be emphasized. In the group of eighteen cases (table 1) treated in the usual manner there were four deaths. Only one death (case 22) occurred in the twenty-three cases (table 2) treated with roentgen rays. This occurred in a child who was just recovering from measles, and had evidence of bronchopneumonia at the time the treatment was given. In this child the local manifestations of the erysipelas disappeared within thirty hours after the treatment but the toxic signs persisted with eventual death, due, in our opinion, to bronchopneumonia. In the group of control cases, the period of elevated temperature varied from two to eleven days, the average being five days. In contrast to this, almost all the patients treated by our method (roentgen ray) had a normal temperature in from one to two days (range 1-3 days) after the treatment was given. The temperature in the majority of cases dropped to normal within twenty-four hours. Likewise, the symptoms, such as pain, toxicity and general malaise, disappeared within one to two days after the roentgen-ray treatment, whereas in cases treated by local application a longer period was required.

Practically all the control cases showed a spreading of the process to contiguous parts of the skin after the treatment was begun. Of the patients treated with roentgen rays only, one patient (case 11) showed extension and this was very slight. Likewise, there was only one case (case 4) in this series in which a complication occurred, a suppurative cervical adenitis which healed rapidly after incision. In case 16, otitis media was present before the onset of the erysipelas and consequently it was not considered as being a complication. In this case the temperature remained elevated after the disappearance of the erysipelas, owing, no doubt, to the otitis media. Three patients (cases 19, 20 and 21) treated with roentgen rays did not show such satisfactory results but they are not considered with the remainder of the group because of certain complicating factors existing before the treatment was given or because other forms of treatment had been instituted previously. Two of them (cases 19 and 20) were inadequately treated as they were among the first patients on whom the roentgen-ray method was used. Case 20 had a puerperal infection before the onset of the erysipelas and developed septicemia, which may have been due to the pelvic disease; mercuro-

TABLE 2.—*Data from Twenty-Three Patients with Erysipelas Treated by Roentgen Rays*

Case*	Age	Duration at Time of Treatment, Days	Temperature	Extent of Infection	Degree of Infection	Time from Treatment to Normal Temperature, Days	Time to Normal Symptoms, Days	Extension After Treatment	Complications and Sequelae	Duration from Treatment to Cure, Days	Duration Whole Illness, Days
1	44	6	101.4	Nose, ears, cheeks	Moderate	1	1	No	None	4	10
2	60	17	103.4	Face, ears, forehead	Severe	1	1	No	None	2	19
3	60	2	103.4	Face, ears	Severe	1	1	No	None	3	5
4	44	8	Nor.	Face	Mild	..	2	No	Abscess †	3	11
5	38	2	102.0	Face, ears, spreading	Moderate	2	2	No	None	3	5
6	57	2	100.4	Face, forehead	Moderate	1	1	No	None	2	4
7	55	4	101.0	Cheek, ear	Moderate	1	1	No	None	2	6
8	59	5	99.2	Face, ears	Moderate	2	2	No	None	3	8
9	39	2	Nor.	Face, forehead	Mild	..	1	No	None	3	5
10	34	2	Nor.	Nose, cheeks	Mild	..	1	No	None	2	4
11	37	6	99.4	Face	Mild	1	1	Slight to neck	None	3	9
12	27	2	100.4	Nose, cheek	Moderate	1	1½	No	None	5	7
13	26	2	101.0	Nose	Mild	1	1	No	None	3	5
14	43	3	101.0	Nose, cheeks	Moderate	1½	1	No	None	4	7
15	65	2	103.0	Face	Severe	1½	1	No	None	3	5
16	2	5	102.2	Face, ear	Moderate	‡	1½	No	Otitis ‡	2	7
17	30	2	102.0	Face, ear	Moderate	1	2	No	None	3	5
18	27	3	Nor.	Face	Mild	..	1	No	None	2	5
19	24	6	104.0	Face, spreading	Severe	4	2	Scalp, neck	Arthritis	4	10
20	22	2	104.6	Buttocks, perineum	Severe	§	§	Legs	Septicemia	..	..
21	25	3	102.0	Face	Moderate	3	2	Scalp	Infected eye	5	8
22	11 mo.	2	104.4	Face, scalp	Extreme	..	..	None	Pneumonia, death	..	..
23	26	14	102.2	Face	Severe	1½	2	No	None	4	18

* In case 19 inadequate treatment was given and had to be repeated; ice packs also were used. In case 20 the patient had a puerperal infection and septicemia developed; mercurochrome-220 soluble also was used; inadequate treatment was given. In case 21 inadequate treatment was given and magnesium sulphate packs were used. The bronchopneumonia in case 22 was a complication of measles which the patient had just passed through; it was present before treatment. Patient 23 was treated in the routine manner without improvement for seven days before irradiation therapy was given.

† This was a suppurating gland which healed after incision.

‡ The otitis media was present before the onset of erysipelas and continued to produce temperature after erysipelas had disappeared.

§ The temperature continued for a long period of time because of puerperal infection and septicemia.

chrome-220 soluble was also used in this case. In cases 19 and 21 ice packs were used together with the roentgen rays, thus confusing the results.

It is difficult to determine the exact time when the disease has completely receded. Some redness and desquamation often persist after the temperature is normal. We considered a patient cured when the redness and swelling were practically gone and the patient was well enough to be up and walking about. Some desquamation usually was still present at this time. Taking this as a criterion, we found that the duration of the disease from the time of roentgen-ray treatment to clinical cure was

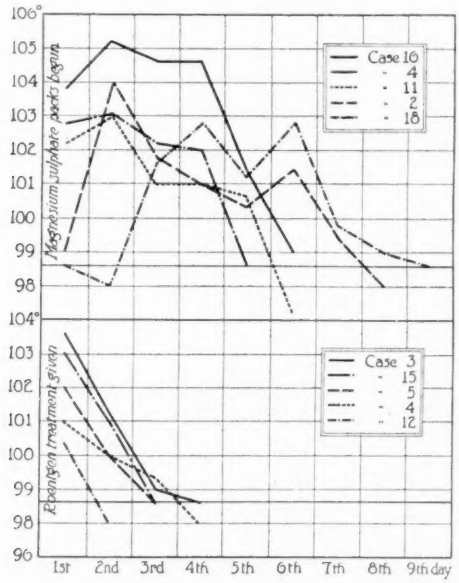

Chart 1.—Comparative temperature charts of five average patients treated with magnesium sulphate packs and of five average patients treated with roentgen rays: The unirradiated cases are shown above, the case numbers referring to table 1; the irradiated cases are shown below, the case numbers referring to table 2; the highest temperature only is recorded for each day; the record is begun on the day when treatment was first given and ended on the first day of normal temperature; the lower temperatures and shorter temperature period of the irradiated patients is well shown.

from two to five days, with an average of three days in the irradiated cases. In the routinely treated cases, it varied from four to twenty-one days, with an average of more than nine days. The duration of the whole illness is also given in the tables but has little significance as the duration of the disease at the time of treatment varied so widely.

The temperature record of five average patients treated in the usual manner and five average patients treated with roentgen rays is shown in chart 1. Only the highest temperature of each day is recorded and the chart is begun on the day when the treatment was first given and ended on the day of the first normal temperature. This shows graphically the much milder and shorter course in the irradiated cases. In chart 2 is shown a more detailed temperature record of patient 23 who was given iced magnesium sulphate and glycerin packs for seven days, with spreading of the infection and no relief. One roentgen-ray treatment was then given with a marked change for the better within twenty-four hours. This patient seemed to be much worse at the time the radiation was given than at any previous time.

When these patients were looked at in a general way, without regard to details of temperature and clinical course, it was apparent to all those who were in contact with them, that the patients receiving roentgen-ray

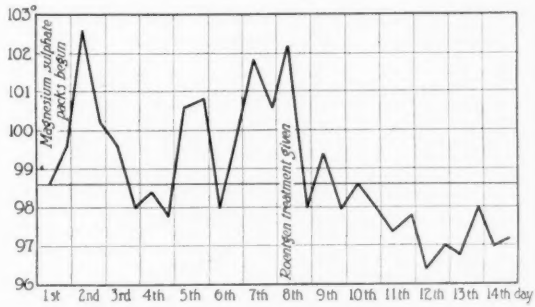

Chart 2.—Complete temperature record of patient 23 treated by the usual methods without success followed by roentgen-ray treatment on the eighth day after entrance; the marked change in the course of the temperature is obvious.

treatment improved far more rapidly than the patients receiving routine treatment for erysipelas. Although it is possible that there were more severe cases in the control group than in the irradiated one, nevertheless there were a number of cases with a serious outlook in the latter series. The average age of the two groups did not differ materially. There were a number of patients of advanced age with chronic alcoholism in the group that had received roentgen-ray treatment, in which the prognosis ordinarily would be grave. It was surprising to see how rapidly these patients became well.

The possibility of deleterious effects of the irradiation on the skin or hair must be considered. In no case was there even the slightest tanning of the skin or any other effect that could be assigned to the irradiation. In two cases there was a temporary loss of hair but this may occur following erysipelas of the scalp without irradiation. It appears

that erysipelatous skin is more resistant to irradiation than the normal skin.

It is difficult to determine the actual cause of the beneficial effect that we have observed. It appears reasonable to assume that it is due to some change in the circulation, possibly to the capillary effect which has recently been described by Pohle.[7]

SUMMARY AND CONCLUSIONS

The present methods of treatment of erysipelas are distinctly unsatisfactory and accomplish little.

Roentgen-ray therapy applied to the affected part produces a rapid improvement in both the local and the systemic manifestations, with a reduction of temperature to normal in from one to two days.

In a group of cases treated by the routine methods and a similar group treated by roentgen-ray irradiation, the vastly superior results in the irradiated group are shown.

Treatment with the roentgen ray is an effective method for shortening the course and decreasing the morbidity and mortality in erysipelas.

7. Pohle, E. A.: Radiology **6**:236, 1926.

A MODIFICATION OF THE UREA CONCENTRATION TEST *

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Many attempts have been made in recent years to develop a satisfactory test for the urea function of the kidney. Ambard presented his coefficient of urea excretion and F. C. McLean introduced the McLean index, which utilized the principles of Ambard's formula but simplified them. H. MacLean and de Wesselow [1] brought out the urea concentration test. Addis [2] studied the ratio between the one hour urine urea and the urea in 100 cc. of blood and Rabinowitz employed the urea concentration factor $\frac{\text{mg. urea in 100 cc. urine}}{\text{mg. urea in 100 cc. blood}}$

Various investigators have shown that urea excretion in normal persons depends on the blood urea concentration as well as on the renal efficiency and also that the concentration of urea in the urine in normal persons can be increased indefinitely, under conditions compatible with life, by increasing the blood urea concentration. It has been further proved that the volume of water excreted has only a slight effect on urea excretion when the blood urea is not increased and that when the blood urea is increased the volume of water excreted which can influence the excretion of urea is between 2.5 and 6 liters; over this amount no influence is possible.

It is essential that a functional test be readily available as well as accurate in order that it may be useful. The urea concentration test has enjoyed wide use in Great Britain but in this country its use has not been attended with success. The test is available, but its accuracy must be questioned. As described by MacLean and de Wesselow the procedure is as follows:

It is best performed in the morning. The patient is instructed not to eat after dinner the night before so that the stomach may be empty. The bladder is emptied. The patient ingests 150 cc. of water flavored with

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* Read before the section on medicine, College of Physicians, Philadelphia, March, 1925.

* From the departments of medicine and physiologic chemistry, Jefferson Medical College Hospital.

1. MacLean, H., and de Wesselow, O. L. V.: Brit. J. Exper. Path. **1**:53 (Feb.) 1920.

2. Addis, T., and Foster, Marjorie: Concentrating Capacity of Kidney, Arch. Int. Med. **34**:462 (Oct.) 1924. Addis, T.: Renal Function and Amount of Functioning Tissue, Arch. Int. Med. **30**:378 (Sept.) 1922.

tincture of orange in which 15 Gm. of urea have been dissolved. The urine is collected one and two hours later and if the second specimen is more than 150 cc., a third hour specimen is taken. The urea concentration is measured in the second or third hour specimen by the Marshall urease method. MacLean places the normal concentration at 2 per cent. A mild loss of function is indicated by a concentration of 1.8 per cent

Chart 1.—A comparison of the normal and nephritic percentage of variation between the two levels when the resting level is below 1 per cent.

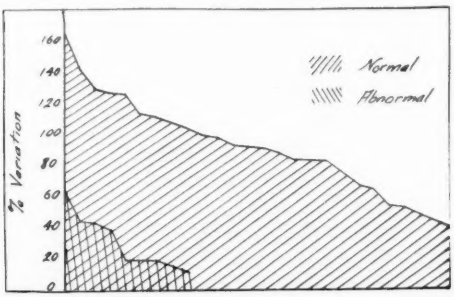

Chart 2.—A comparison of the normal and nephritic percentage of variation between the two levels when the resting level is from 1 to 1.5 per cent.

and more severe grades by concentrations of 1.6 per cent or lower. MacLean states that this test yields a more accurate estimation of functional renal impairment than any other. E. Weiss found that the results paralleled those obtained with the phthalein test and stated that it was valuable in the diagnosis of early nephritis.

Like most tests of renal function the urea concentration test fails in certain instances to denote accurately the degree of renal damage and in the following conditions often fails to give evidence of renal damage. In chronic nephritis with salt and water retention it is not uncommon to find a urine urea concentration of 2 per cent or above. Certain patients with symptoms of severe renal damage were studied in whom the urea concentration was 1.5 or 1.6 per cent. The kidneys of these patients at necropsy showed almost complete loss of functioning tissue. The urea concentration should have been much lower. A considerable number of

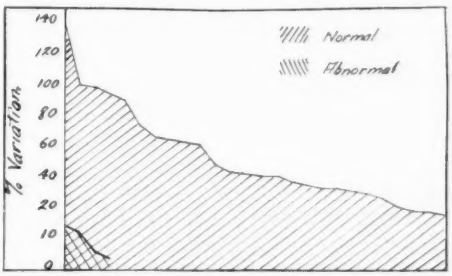

Chart 3.—A comparison of the normal and nephritic percentage of variation when the resting level is from 1.5 to 2 per cent.

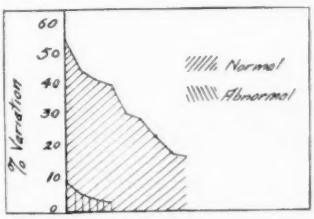

Chart 4.—A comparison of the normal and nephritic percentage of variation when the resting level is 2 per cent or above.

patients have been studied who had a high blood urea and whose urine urea concentration was 2 per cent. Any test in which the difference between abnormal and normal urine urea varies only by 0.2 per cent must be open to wide possibilities of error.

We concluded from the results obtained with this test that in severe nephritis the urine urea concentration would be almost the same following the ingestion of water alone as that following the ingestion of water plus urea. We felt that there must be a definite response of the normal kidney to the ingestion of urea and that a failure of response might indicate degrees of renal impairment. We termed the urine urea concentra-

Case	Age	Diagnosis	Urine Examinations: Quantity, Cc.	Urine Examinations: Specific Gravity	Urine Examinations: Albumin	Urine Examinations: Casts	Phenolsulphonphthalein, per Cent	Urea Concentration: Rest Levtl, per Cent	Urea Concentration: Urea Response Level, per Cent	Urea Concentration: Percentage of Variation	Blood Chemistry: Non-protein Nitrogen	Blood Chemistry: Urea Nitrogen, Mg.	Blood Chemistry: Creatinine	Blood Pressure	
1	..	.....	.....	1.016 to 1.022	+++	Many granular	40	0.23	0.515	121	....	34	1.9	200 - 170 / 130 - 100	
2	69	Chronic interstitial nephritis	1,500	1.010 to 1.015	+++	Many hyaline and granular	25	0.24	0.52	116	46.2	31.8	1.9	200 - 170 / 130 - 100	Condition serious on admission; stuporous; much improved after two weeks
3	39	Chronic interstitial nephritis	850 to 1,750	1.010 to 1.016	+++	Few hyaline	15	0.288	0.6	111	74.07	48.6	3.128	210 - 170 / 140 - 110	Condition serious; headache, dizziness, weakness; unimproved
4	21	Chronic nephritis with edema	1,000 to 3,500	1.012 to 1.028	++++	Few hyaline and granular	55	0.35 1.38	0.2 2.10	—43 +52	54.5 28	31 16.2	2.3 1.5	140 / 90	Moderate edema of legs; greatly improved general condition following tonsillectomy
5	43	Chronic interstitial nephritis	2,500 to 3,000	1.004 to 1.010	+++	Many hyaline and granular	35	0.36	0.88	144	45	2.7	1.9	160 - 180 / 100 - 120	Severe headache; dyspnea; unimproved
6	37	Chronic diffuse nephritis; tonsillitis	500 to 1,300	1.010 to 1.023	+++	Few hyaline and granular	25	0.4	0.3	—25	37.7	17.3	1.58	210 - 146 / 130 - 94	Severe headache and dizziness; rapid improvement following tonsillectomy
7	17	Chronic interstitial nephritis	600 to 900	1.010 to 1.015	+	0	25	0.492	1.2	177	28.6	13.8	1.56	120 - 110 / 70 - 60	Condition good; no severe symptoms; discharged improved
8	23	Chronic diffuse nephritis	250 to 500	1.009 to 1.017	+++	Few hyaline and granular	15	0.55	0.6	18	55	38	2.4	180 / 120	Headache, vomiting, edema; toxic; stuporous on admission; died
9	31	Chronic interstitial nephritis	2,500 to 4,000	1.002 to 1.012	++++	Many hyaline and granular	40	0.648	0.528	—18	33	20.2	1.8	140 - 100 / 90 - 50	Severe vomiting; polyuria; improved after tonsillectomy
10	47	Cardiac decompensation; pulmonary tuberculosis	1,000 to 1,800	1.012	++	Occasional hyaline	..	0.72	1.14	58	....	....	....	90 100 / 50 60	Dyspnea, edema; severe decompensation with passive congestion
11	27	Rheumatic fever, acute nephritis	700 to 1,100	1.020 to 1.030	+	0	..	0.88	1.2	47	....	....	....	120 / 90	Very mild attack of nephritis; discharged well
12	69	Chronic diffuse nephritis; myocarditis	300 to 2,100	1.010 to 1.030	+	Occasional	25	0.9	1.15	28	27.5	14.16	1.53	210 - 163 / 110 - 78	Orthopnea; edema of legs; confusion; passive congestion of liver; improved
13	19	Chronic nephritis with edema	1,000 to 1,500	1.009 to 1.026	+	Few hyaline and granular	15	1	1.2	20	28.56	15.2	1.58	120 / 60	Edema of feet and face; no subjective symptoms; condition unchanged
14	17	Chronic parenchymatous nephritis	500 to 1,300	1.014 to 1.025	++++	Many hyaline and granular	20	1	1.2	20	57.1	31	2.12	120 - 170 / 80 - 130	Greatly edematous and dyspneic; rapid improvement on salt-free diet

Urine and Blood Examinations—Continued

15	55	Arteriosclerosis; hypertension	650 to 1,500	1.009 to 1.014	+	Occasional hyaline	45	1.02	1.2	17	40	22.3	1.7	250 - 145 / 120 - 92	Headache, backache, poor vision; much improved on salt-free diet
16	60	Chronic nephritis with edema	600 to 900	1.020 to 1.025	++++	Many hyaline and granular	40	1.17	1.94	65	39.6	22.4	2.16	150 - 170 / 100 - 130	Marked edema on admission; rapid improvement on salt-free diet; lost 25 pounds (11.3 Kg.); edema gone
17	45	Chronic nephritis with edema	1,150 to 2,600	1.014 to 1.030	+++	Many hyaline and granular	25	1.2	1.35	12	44.4	26	1.8	180 - 140 / 100 - 70	Edema of feet, ascites, slight dyspnea; edema disappearing; general improvement
18	65	Chronic nephritis; uremia; diabetes	1,000 to 1,200	1.008 to 1.030	+	0	15	1.2	1.68	40	25.8	14.7	1.51	180 - 130 / 110 - 70	Admitted in coma; condition much improved on discharge
19	39	Chronic nephritis; myocarditis; pulmonary tuberculosis	800 to 1,900	1.010 to 1.020	+++	Many hyaline and granular	40	1.2	1.75	46	43.6 31.2	28 16	2.1 1.7	220 - 170 / 150 - 100	Condition moderately severe; slight decompensation; discharged improved
20	21	Acute nephritis	1,000	1.016 to 1.021	++++	Many hyaline and granular	20	1	1.2	20	....	20.6	1.5	145 / 100	Great edema; condition serious; improved and discharged well
21	46	Myxedema	1,100	1.020 to 1.028	+	0	..	1.22	1.76	44	28.6	15.2	1.63	170 - 130 / 100 - 80	Discharged improved
22	29	Chronic pulmonary tuberculosis; chronic tonsillitis; chronic nephritis	1,150 to 1,400	1.008 to 1.016	++	Occasional hyaline and granular	40	1.6	1.8	12	....	....	....	160 / 110	Serious condition; left hospital unimproved
23	45	Bilateral congenital cystic kidneys	.....	1.008 to 1.015	++	Few hyaline and granular	45	1.6	1.82	14	....	27	....	150 / 100	At postmortem almost complete absence of normal renal tissue
24	62	Chronic diffuse nephritis; pernicious anemia	900 to 1,300	1.020	+	0	45	1.8	1.9	6	49.8	29.2	1.7	130 / 90	Condition serious; unimproved on discharge
25	17	Acute nephritis; infectious enterocolitis	950 to 1,850	1.008 to 1.015	+	Many hyaline and granular	40	2.37	2.44	3	....	18	....	130 / 95	Severe diarrhea following appendectomy; well on discharge
26	18	Acute tonsillitis; acute nephritis	800 to 1,200	1.023	+++	Occasional hyaline and granular	45	2.42	2.66	10	....	....	....	140 - 90 / 60 - 50	Condition very mild; discharged well after tonsillectomy
27	18	Chronic nephritis; splenic anemia	750 to 8,250	1.010 to 1.018	++	Few granular	30	2.76	2.88	4	28.6	16.43	1.61	80 - 100 / 20 - 40	Serious condition; marked anemia; hemorrhage from gastrointestinal tract
28	26	Acute lead poison	900 to 1,900	1.014 to 1.020	+	0	35	8.54	3.78	6	....	14.2	....	140 / 100 160 / 98	Severe colic, nausea, vomiting; constipation much improved on discharge
29	31	Mitral stenosis; pulmonary tuberculosis	1,000 to 1,600	1.015 to 1.020	++++	Few hyaline and granular	..	0.45	1.2	166	....	....	....	120 - 110 / 80 - 60	Moderate decompensation; improved
30	32	Pyelitis; chronic suppurative nephritis	960 to 1,200	1.010 to 1.020	+	0	45	0.48	1.32	175	28.5	16.2	1.57	120 - 140 / 80 - 90	One kidney formerly removed; many pus cells; chills, fever; improving under treatment

tion after water alone "resting level," and after water plus urea "urea response level." The following technic is used:

The patient should be instructed to eat nothing after the evening meal.
7 a. m. 150 cc. of water should be ingested.
8 a. m. The first specimen of urine should be collected.
9. a. m. The second specimen of urine should be collected.
9 a. m. 150 cc. of water flavored with tincture of orange in which 15 Gm. of urea is dissolved should be ingested.
10 a. m. The third specimen of urine is collected.
11 a. m. The fourth specimen of urine is collected. If the fourth specimen is greater in amount than 150 cc., a fifth specimen (at 12 noon) is collected.
The urea concentration in the second and fourth specimens is estimated by the Marshall urease method.

Ninety-three normal students and thirty patients with nephritis were studied by this method. The results of both the normal and the abnormal cases are divided into five groups:

1. Those with a resting level urea concentration between 0 and 0.5 per cent. There were four in this group. The resting level and the urea response level concentration varied 684 per cent.

2. Those with a resting level urea concentration (following water alone) between 0.5 and 1 per cent. There were twenty-one in this group. The resting level urea concentration and the urea response level urea concentration varied 210 per cent.

3. Those with a resting level urea concentration between 1 and 1.5 per cent. There were thirty-one in this group. The percentage variation was 98 per cent.

4. Those between 1.5 and 2 per cent. There were twenty-eight in this group. The percentage variation was 47.8 per cent.

5. Those with a concentration of 2 per cent or more. There were nine in this group. The percentage variation was 38 per cent.

In normal persons, the lower the resting level urea concentration the greater the variation between it and the urea response level concentration. The higher the resting level, the less the percentage variation between it and the urea response level.

There were seven nephritic cases in group 1. The percentage variation was 90 per cent; in normals it was 684 per cent.

There were seven cases in group 2. The percentage variation between the resting level concentration and the urea response level was 30 per cent. In normal persons it was 210 per cent.

There were nine patients in group 3 with a resting level between 1 and 1.5 per cent. The percentage variation was 25.5 per cent and in the normal persons it was 98 per cent.

There were three cases in group 4 with a resting level of from 1.5 to 2 per cent. The percentage variation was 11 per cent and in normal persons it was 48 per cent.

There were four patients in group 5 with a resting level of 2 per cent or above. The percentage variation was 5.4 per cent and in normal persons it was 38 per cent.

The degree of functional impairment may be proportional to the lessened amount of variation between the two levels. Little variation between the two levels when the resting level concentration is high, between 1.6 and 2 per cent, may be more indicative of renal impairment than a greater percentage of difference when the resting level concentration is low.

In chronic nephritis with water or salt retention the urea concentration may be 2 per cent or above but the functional impairment present is

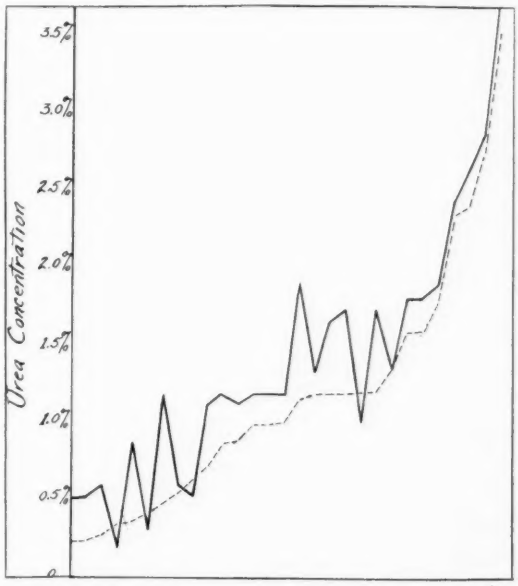

Chart 5.—The variation between the two levels in thirty-one patients with nephritis; solid line: urea response level; broken line: resting level.

shown by a percentage variation between the two levels that is less than normal. Two patients may have concentrations between 1 and 1.5 per cent. In one there may be considerable variation between levels and in the other little or none. The one with the less variation has the greater functional impairment. Functional improvement is shown by an increase in variation between levels in successive tests.

In those cases in which the phthalein test is between 45 and 55 per cent the absence of normal variation between the two levels denotes the presence of functional impairment.

COMMENT

This modification of the urea concentration test is offered to remedy some of the fallacies of the test as heretofore described. The test is readily available and increases the accuracy of the interpretation of changes in urea elimination. If the urea concentration test is to be used it seems better to consider the results from the standpoint of variation between a resting level urea concentration and urea response level concentration than from the urea concentration alone. This report does not include work on any great variety of renal cases and we are not able to state to what extent we may rely on lack of variation to indi-

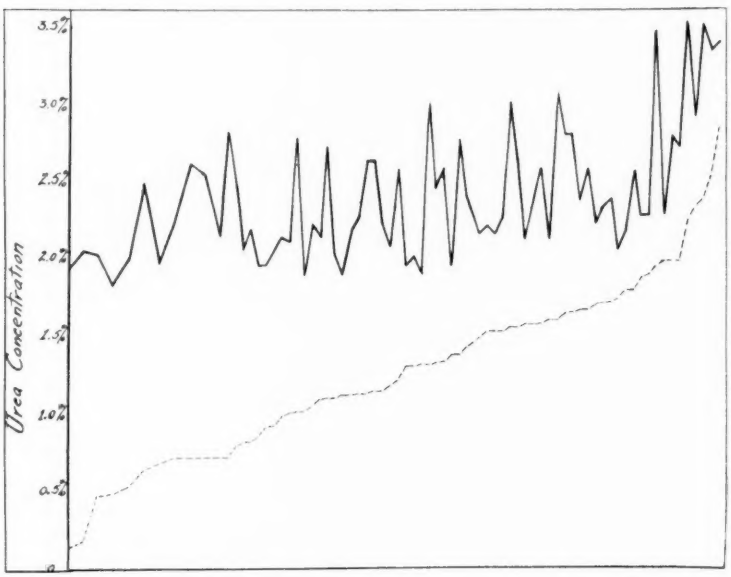

Chart 6.—The variation between the two levels in ninety-three normal students; broken line: resting level; solid line: urea response level.

cate varying degrees of renal insufficiency. It seems, however, that the results obtained would indicate that this modification demonstrates with much greater certainty the presence of renal change in a given patient than does the old urea concentration test.

CONCLUSIONS

In a modification of MacLean's urea concentration test the percentage variation between resting level concentration and urea response level concentration is shown to be more significant of renal damage than urea response level concentration alone.

Ninety-three normal persons and thirty patients with nephritis have been studied. They are divided into five groups.

Group 1 includes those with a resting level between 0 and 0.5 per cent. The normals varied 684 per cent; the nephritic patients varied 90 per cent.

Group 2 includes those with a resting level concentration between 0.5 and 1 per cent. The normals varied 210 per cent; the nephritic patients varied only 30 per cent.

Group 3 includes those with a resting level urea concentration of from 1 to 1.5 per cent. The normals varied 98 per cent; the nephritic patients varied only 25.5 per cent.

Group 4 includes those with a resting level urea concentration of from 1.5 to 2 per cent. The normals varied 47.8 per cent; the nephritic patients varied 11 per cent.

Group 5 includes those with a resting level urea concentration of 2 per cent or above. The normals varied 38 per cent; the nephritic patients varied 5.4 per cent.

Functional improvement is shown by an increase in variation between the two levels when the test is repeated.

In some instances the phthalein test failed to denote the evident renal impairment, yet the lessened percentage variation was comparable to the functional loss as indicated by physical symptoms.

THE BASAL METABOLISM OF THE JAPANESE*

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As a result of the greatly increased interest in the basal metabolism of human subjects, important contributions on the metabolism of normal Americans and Europeans have been made by various workers, while we have been unable to find any metabolism measurements of normal Japanese until recent years. The first article published on this subject was perhaps that presented by some of us [1] at the regular meeting of the Temporary Beriberi Investigating Committee, Oct. 28, 1922, and at the general meeting of the Tokyo Igakkai. The investigation was made under the direction of Prof. R. Inada on twenty-five students, aged from 22 to 28. The conclusion of this preliminary report was that the basal metabolism of healthy Japanese is quite in accordance with that of Americans and Europeans although the climate, humidity, the conditions of living and physical characteristics are remarkably different from those of Western people.

At an early date Eijkmann,[2] working in Batavia, could find no significant change in the basal metabolism of the Malays. Using a Zuntz-Geppert apparatus he studied twelve Malay servants accustomed to light work, eleven Europeans living in Batavia, rather heavier than the Malays, and compared these with the normal men studied in Germany by Geppert, Loewy and Magnus-Levy. The oxygen consumption of normal Germans, weighing on the average 62 Kg., was 250.3 cc. per minute and that of Malays was 251.5 cc. calculated for the same weight; that of Europeans living in Batavia was 245.7 cc.

Fleming,[3] in making observations on eight normal Filipinos, reported that all had a basal metabolic rate below the normal standard, the average deviation being —5.3 per cent. The subjects, however, were all surgical convalescents so that these data were for so-called hospital normals.

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1. Okada, S.; Sakurai, E.; Ibuki, T., and Kabeshima, H.: Ikai Jiho, no. 1479, Nov. 4, 1922.
2. Eijkmann, C.: Arch. f. d. ges. Physiol. **64**:57, 1896.
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Takahira [4] in January, 1925, made a report of the basal metabolism of 120 Japanese men and women from the Imperial Nutrition Institute of Japan and concluded that the basal metabolism of the Japanese shows no remarkable difference from that of Europeans and Americans.

MacLeod, Crofts and Benedict [5] measured the basal metabolism of nine normal Oriental women, seven Chinese and two Japanese, ranging in age from 21 to 29 years, and found that it was in most cases strikingly low, on the average being 10.4 per cent below the Harris and Benedict prediction standard. Comparisons with the Aub and Du Bois and the Dreyer standards gave essentially the same picture, i. e., a persistently low metabolism in these orientals.

From the foregoing data it may be seen that there are two different views of the basal metabolism of orientals. On the one hand, it is proved that the basal metabolism of orientals is quite in accordance with that of Western people; others state that a persistently low metabolism exists. It is most important, therefore, to determine this point exactly and whether the Western standards may be applied to the orientals directly or not.

OBSERVATIONS AND TECHNIC

Our studies were made on students and nurses who were quite healthy and retained their usual dietary habits and general habits of life. The measurements were made in the postabsorptive condition, that is, at least twelve hours, usually from fourteen to eighteen hours after the last meal, with avoidance of muscular activity and with due regard to the importance of psychic repose. The experiments were made in spring, summer and autumn, i. e., in every season except the extremely cold winter. The experimental evidence shows that no essential difference exists in the basal metabolism at different seasons. The physiologic observations included for students the pulse rate, respiration rate and temperature and for nurses vital capacity, systolic and diastolic blood pressure in addition. Records for age, height and weight are made as usual. The surface areas are calculated by the Du Bois height-weight formula [6] and partly by using the nomographic chart of Boothby and Sandiford.[7] In tables 1 and 2 are shown also the surface areas calculated by the formulas derived by Boothby and Sandiford [8] from the

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5. MacLeod, G.; Crofts, E. E., and Benedict, F. G.: Am. J. Physiol. **73**:463 (July) 1925.

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7. Boothby, W. M., and Sandiford, R. B.: Boston M. & S. J. **185**:337 (Sept. 22) 1921.

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TABLE 1.—*Data for Normal Males*

Case	Age	Height in Cm.	Weight in Kg.	Surface Area: Du Bois Height-Weight Formula, Sq. Meters	Surface Area: Harris and Benedict Formula, Sq. Meters	Pulse Rate	Respiration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate: Du Bois Standards, per Cent	Basal Metabolic Rate: Harris and Benedict Standards, per Cent
1	23	159.3	44.4	1.42	1.40	56	16	147	209	0.74	1,370	40.2	+ 1.7	+ 3.9
2	24	158.0	51.4	1.50	1.50	49	20	159	189	0.84	1,313	36.5	— 8.2	— 6.3
3	28	159.0	47.5	1.46	1.44	68	9	169	187	0.90	1,325	37.8	— 4.3	+ 0.7
4	25	158.8	53.2	1.53	1.53	60	12	172	211	0.81	1,465	39.9	+ 1.0	+ 2.8
5	25	162.5	56.7	1.60	1.67	80	16	188	209	0.90	1,486	38.7	— 2.0	— 0.3
6	25	162.5	47.8	1.49	1.47	54	12	174	205	0.85	1,438	40.2	+ 1.8	+ 5.1
7	24	165.3	46.9	1.46	1.47	72	17	158	169	0.95	1,216	34.7	—12.2	—11.6
8	24	162.0	52.3	1.54	1.53	54	16	160	205	0.78	1,408	38.1	— 3.6	— 1.8
9	25	163.2	51.8	1.55	1.53	74	12	157	209	0.75	1,428	38.4	— 2.8	0.0
10	24	160.7	47.7	1.47	1.46	58	17	165	198	0.83	1,394	39.5	0.0	+ 3.9
11	25	157.5	61.3	1.62	1.64	60	16	185	216	0.86	1,520	39.1	— 1.0	— 0.6
12	24	158.9	35.7	1.29	1.27	72	18	134	148	0.91	1,053	34.0	—13.9	—11.5
13	25	160.5	55.2	1.57	1.56	58	15	171	205	0.83	1,436	38.1	— 3.6	— 1.6
14	24	165.5	55.2	1.60	1.59	72	13	166	194	0.86	1,369	35.6	— 9.8	— 8.2
15	25	170.9	52.5	1.61	1.60	66	16	174	209	0.83	1,461	37.8	— 4.3	— 0.9
16	24	160.8	54.8	1.57	1.56	56	17	188	209	0.90	1,492	39.6	+ 0.3	+ 2.1
17	22	158.6	47.6	1.46	1.44	78	17	158	214	0.74	1,461	41.7	+ 5.6	+ 0.3
18	24	165.5	59.1	1.65	1.64	65	17	198	248	0.80	1,712	43.2	+ 9.3	+10.8
19	24	157.8	49.8	1.49	1.47	76	15	182	221	0.82	1,538	43.0	+ 8.9	+11.5
20	24	163.1	51.1	1.54	1.52	60	13	169	219	0.77	1,501	40.6	+ 2.8	+ 7.9
21	27	167.6	49.8	1.55	1.52	58	13	166	185	0.90	1,320	35.5	—10.1	— 6.3
22	23	160.4	46.5	1.45	1.44	80	16	164	180	0.91	1,270	36.5	— 7.6	— 6.1
23	24	161.0	43.9	1.43	1.40	60	17	159	192	0.79	1,318	38.4	— 2.8	+ 0.3
24	25	165.5	65.5	1.73	1.74	56	14	178	226	0.79	1,557	37.5	— 5.1	— 4.2
25	25	159.0	55.5	1.56	1.56	60	8	179	226	0.79	1,552	43.1	+ 9.1	+ 6.6
26	26	160.5	52.8	1.54	1.53	60	16	125	177	0.71	1,194	32.3	—18.2	—15.9
27	24	161.5	51.1	1.52	1.51	68	13	168	182	0.92	1,299	35.6	— 9.9	— 8.2
28	24	152.5	46.6	1.41	1.40	78	18	129	183	0.71	1,238	56.6	— 7.4	— 5.4
29	25	177.5	68.5	1.85	1.85	59	20	214	264	0.81	1,820	41.0	+ 3.8	+ 5.3
30	22	167.1	53.4	1.57	1.57	62	15	151	212	0.71	1,436	38.1	— 3.6	— 4.3
31	22	158.0	48.3	1.47	1.45	62	14	148	191	0.77	1,312	37.2	— 5.8	— 5.3
32	23	162.7	56.0	1.60	1.59	54	19	158	213	0.74	1,448	37.7	— 4.6	— 3.1
33	28	162.2	50.0	1.52	1.50	69	14	166	214	0.78	1,481	40.6	+ 2.8	+ 7.6
34	24	161.0	53.2	1.55	1.54	69	13	185	201	0.92	1,436	38.6	— 2.3	— 3.3
35	22	162.3	49.6	1.51	1.49	76	16	189	231	0.82	1,605	44.3	+12.2	+12.7
36	22	161.5	51.7	1.53	1.52	64	15	171	213	0.80	1,469	40.0	+ 1.3	+ 1.4
37	22	162.8	50.3	1.52	1.51	52	10	173	207	0.84	1,445	39.6	+ 0.3	+ 0.6
38	24	166.4	55.0	1.61	1.59	74	17	177	229	0.77	1,569	40.6	+ 2.8	+ 5.1
39	25	163.3	49.6	1.52	1.50	59	17	163	229	0.71	1,521	41.7	+ 5.6	+ 9.7
40	24	157.5	57.8	1.58	1.59	68	16	182	203	0.89	1,440	38.0	— 3.8	— 3.1
41	24	155.7	53.2	1.51	1.51	58	22	157	220	0.71	1,479	41.2	+ 4.3	+ 4.5
42	23	167.2	47.6	1.51	1.49	70	17	146	188	0.78	1,295	35.7	— 9.6	— 7.6
Average	24	161.9	51.85	1.53	1.526	64	13	169	205	0.82	1,246	38.7	— 2.0	— 0.2

TABLE 2.—*Data for Normal Females*

Case	Age	Height in Cm.	Weight in Kg.	Surface Area: Du Bois Height-Weight Formula, Sq. Meters	Surface Area: Harris and Benedict Formula, Sq. Meters	Pulse Rate	Respiration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate: Du Bois Standards, per Cent	Basal Metabolic Rate: Harris and Benedict Standards, per Cent
1	22	153.1	52.0	1.47	1.50	90	21	151	189	0.80	1,312	37.2	+ 0.5	— 1.5
			52.5	1.47	1.51	62	18	149	179	0.83	1,235	35.0	— 5.4	— 7.6
2	22	150.5	51.0	1.44	1.49	66	19	152	177	0.86	1,220	35.3	— 5.1	— 7.4
			52.5	1.45	1.50	60	17	143	186	0.77	1,274	36.6	— 2.7	— 4.4
3	21	148.0	45.0	1.35	1.42	78	18	132	186	0.71	1,257	38.8	+ 4.8	— 0.3
			44.5	1.35	1.41	72	19	152	187	0.80	1,290	39.8	+ 7.5	+ 2.7
4	22	154.7	62.5	1.61	1.62	60	19	168	233	0.72	1,569	40.6	+ 9.7	+ 9.3
			61.5	1.60	1.61	60	14	168	216	0.78	1,486	38.7	+ 4.3	+ 4.1
5	20	140.6	45.5	1.31	1.41	72	14	147	171	0.86	1,195	38.0	+ 2.7	— 4.9
			45.5	1.31	1.41	80	12	143	152	0.94	1,088	34.6	— 6.5	—13.4
6	20	147.5	48.5	1.40	1.46	66	14	146	183	0.80	1,257	37.4	+ 1.0	— 3.1
			48.5	1.40	1.46	58	14	143	166	0.86	1,159	34.5	— 6.7	—10.7
7	21	153.0	40.5	1.33	1.38	60	11	145	175	0.83	1,213	38.0	+ 2.7	— 1.1
8	21	148.8	47.0	1.38	1.44	72	10	120	141	0.85	1,033	31.2	—15.6	—19.4
			47.5	1.39	1.44	60	12	107	148	0.72	1,064	31.9	—13.8	—17.2
9	21	150.1	47.0	1.39	1.44	78	14	161	178	0.79	1,228	36.8	— 0.5	— 4.3
			47.0	1.39	1.44	66	12	132	184	0.72	1,241	37.2	+ 0.5	— 3.3
10	21	150.8	57.5	1.52	1.56	84	13	157	194	0.81	1,339	36.7	— 0.8	— 3.4
			56.5	1.51	1.55	78	8	152	200	0.76	1,363	37.6	+ 1.6	— 0.9
11	20	149.2	45.5	1.37	1.42	72	15	129	184	0.70	1,240	37.7	+ 1.9	— 2.6
			45.5	1.37	1.42	90	14	163	177	0.92	1,259	38.3	+ 3.5	— 1.1
Average	21	150.5	50.0	1.43	1.47	70	15	146	181	0.81	1,258	36.75	— 0.7	— 3.9

Harris and Benedict formulas [9] for the prediction of total calories in men and women.

The metabolic rates are obtained by the open or gasometer method with analysis of the expired air by the Haldane gas analysis apparatus. Two analyses are made of the expired air, and the results are accepted if they agree within 0.04 per cent for carbon dioxide and 0.06 per cent for oxygen; additional analyses are required if there is a greater discrepancy. Repeated outdoor air analyses are made and a very definite routine, described in detail in the laboratory manual of the technic of basal metabolic determinations of Boothby and Sandiford, has been adopted. The cooperation of the subjects is the important factor to get the basal values. The calmness of the subjects usually was proved by repeated measurements of the expired air of five minutes. If great discrepancy and irregularity of the ventilation rates were observed, additional measurements were made until fairly constant values had been obtained. With nervous and restless subjects this procedure is apt to fail and sometimes it takes many days until consistent results are obtained. In some cases the recording apparatus of Krogh was also used parallel with the gasometer method and the results found to agree closely.

RESULTS

Physical Characteristics.—The main observations in this study are shown in the tables. Special consideration should be given to the physical characteristics of the subjects. The normal men were all medical students, ranging in age from 22 to 28, the average age being 24. The average height was 161.9 cm. and the average weight, 51.85 Kg. The normal women were all nurses of the college hospital, ranging in age from 20 to 22, the average age being 21. The average height was 150.5 cm. and the average weight, 50 Kg. Compared with the average data of Americans of the same age (for example, 172 cm. and 64.7 Kg. for males; 161.3 cm. and 59.1 Kg. for females of the Boothby and Sandiford's cases), the relatively small size and shortness of stature of the Japanese are evident. Takahira, who measured with molds, has suggested, however, that the Du Bois height-weight formula for surface area will also be satisfactorily applied to the Japanese. The average surface area for the forty-two normal men, according to the Du Bois height-weight standards, is 1.53 square meters, and according to the Harris and Benedict height-weight standards for men is also 1.53 square meters; for the eleven normal women the Du Bois standards give an average of 1.43 square meters and the Harris and Benedict standards for women 1.47 square meters.

9. Harris, J. A., and Benedict, F. G.: Carnegie Inst. Washington Pub. 279, 1919.

Physiologic Functions.—Vital Capacity: The vital capacity of eleven women ranged from 2.16 to 2.91 liters, being on the average 2.47 liters. West [10] computes that for women the vital capacity in cubic centimeters divided by the height in centimeters equals 20, and that the vital capacity in liters divided by the body surface in square meters is equal to 2. The Teachers College group (thirty-six women) mentioned by MacLeod, Crofts and Benedict showed ratios of 18.3 and 1.86, respectively. In the case of our subjects the vital capacity divided by the height ranged from 15.2 to 19, the average of the eleven subjects being 16.5. The vital capacity divided by the surface area ranged from 1.61 to a maximum of 2.19, the average for the eleven women being 1.76. Another series of seventy-six women (hospital nurses) showed ratios of 16.9 and 1.82, respectively. Thus, based on these American standards, our subjects showed somewhat low vital capacity.

Blood Pressure: The blood pressure of eleven women was determined. The Riva-Rocci sphygmomanometer with the auscultatory method was employed throughout. The systolic pressure ranged from 90 to 113 mm., the average being 101 mm. on the right side; on the left side from 80 to 113 mm., the average being 96 mm. The diastolic pressure ranged from 42 to 80 mm., the average being 64 on the right; on the left side from 42 to 77 mm., the average being 61 mm. The average pulse pressure was 37 mm. on the right side and 35 mm. on the left side.

Pulse Rate: The average pulse rate of the forty-two men studied was 64 beats per minute, the minimum being 52 and the maximum 80. The average pulse rate of the eleven women was 70, the minimum being 58 and the maximum 90. In general the pulse rates of women are higher than those of men. The average pulse rate in a series of normal cases studied by Gephart and Du Bois [11] for men was 62 and for ninety women, whose metabolism data were analyzed by Harris and Benedict, 68. The average pulse rates of eighty-nine normal men and sixty-eight women observed by Benedict and Emmes [12] were 61 and 69, respectively. In view of the fact that our patients were all relatively young, the pulse rates of these Japanese practically coincide with those of the Americans.

Respiration Rate: The average respiration rate of forty-two men was 13 and that of eleven women was 15. When the subjects

10. West, H. F.: Clinical Studies on Respiration; Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

11. Gephart, F. C., and Du Bois, E. F.: Clinical Colorimetry: The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (May) 1915.

12. Benedict, F. G., and Emmes, L. E.: J. Biol. Chem. **20**:253, 1915.

were breathing normally in the room, without masks, the rate was 15 and 17, respectively. Sometimes a pronounced effect of the use of the respiration appliance on the respiration rate was observed. The respiration rate of 8 was noted with subject 25 (male); when this subject was breathing normally in the room, without mask, the rate was 11 respirations a minute. A pronounced alteration in the respiration rate when the mask is used, usually a slowing of the rate, has frequently been noted by us; this is not infrequently noted in the literature.

Temperature: The body temperature of the males ranged from 36 to 37.1 C., the average being 36.4 C.; that of the females ranged from 35.5 to 36.6 C., the average being 36 C. The temperature of the room when the experiment was carried out ranged from 29 to 14.4 C., the average being 22.8 C. in males; in females from 27.2 to 11.4 C, the average being 17.6 C.

Basal Metabolism: In males the oxygen consumption varied from 148 cc. in subject 12 to 264 cc. per minute in subject 29, the average being 205 cc. The carbon dioxide production varied from 125 cc. in subject 26 to 214 cc. in subject 29, the average being 169 cc. The respiratory quotient ranged from 0.71 to 0.95, the average being 0.82. In females the oxygen consumption varied from 141 cc. in subject 8 to 233 cc. in subject 4, the average being 181 cc. The carbon dioxide production varied from 107 cc. in subject 8 to 168 cc. in subject 4, the average being 146 cc. The respiratory quotient ranged from 0.70 to 0.94, the average being 0.81. The range of the total twenty-four hour heat production in males was from 1,052 calories in subject 12 to 1,605 calories in subject 35, the average being 1,426 calories; in females from 1,033 calories in subject 8 to 1,569 calories in subject 4, the average being 1,258 calories. As has already been pointed out, the normal American subjects are taller and heavier on the average than the Japanese, so the total heat production of our subjects is not directly comparable with that of western normals. The basal heat production for males as predicted by Harris and Benedict is

$$h = 66.4730 + 13.7516w + 5.0033s - 6.7550a$$

and for females is

$$h = 655.0955 + 9.5634w + 1.8496s - 4.6756a,$$

in which

a = age in years
h = heat production per twenty-four hours
w = weight in kilograms
s = stature in centimeters

By means of this prediction formula we have predicted from the age, height and weight of our subjects their total twenty-four hour metabo-

lism and compared it with that actually measured. The deviations from these predictions expressed in percentage are also recorded in tables. In this comparison most cases except two, one male and one female, show deviations less than ± 15 per cent from the standards, i. e., 96 per cent of all cases are within ± 15 per cent; forty-six cases, 87 per cent, are within ± 10 per cent. In males nearly the same number are plus and minus while in females more cases are somewhat less than the predicted metabolism. The average heat production predicted by Harris and Benedict is 1,429 calories for males and 1,309 calories for females. The average deviation of the actually measured metabolism from the standards is therefore —0.2 per cent for males and —3.9 per cent for females. The standards of Harris and Benedict for women are believed to be 5 per cent too high, therefore our results coincide fairly well with the commonly accepted standards for Americans.

The standards of Aub and Du Bois [13] for the age range of our subjects, that is, between 20 and 30 years, is 39.5 calories per square meter of body surface per hour for males and 37 calories for females. A comparison of the heat production per square meter of body surface per hour with the Aub and Du Bois standards shows 98 per cent of the whole number of cases to be within ± 15 per cent, 89 per cent within ± 10 per cent of the standards. The average heat production in males per square meter per hour is 38.7 calories, —2 per cent, and of female cases is 36.75 calories, —0.7 per cent of the standards. King [14] proposed to use the carbon dioxide elimination as an index to basal metabolism. For the range of age from 20 to 30 years the normal figures are 12.98 Gm. for men and 11.95 Gm. for women per square meter of body surface per hour. The average carbon dioxide elimination of our males was 12.87 Gm. and of the females, 11.89 Gm. per square meter per hour. The percentage deviation of the former from the standards was therefore —0.8 and of the latter, —0.5.

Krogh,[15] Benedict and others consider that the present standards are probably from 4 to 5 per cent or more too high. Sanborn [16] in his work on basal metabolism has presented a table containing the Du Bois normal standards with 1.8 calories arbitrarily deducted. A comparison of the heat production of our cases with this modified standard also shows nearly the same percentage of cases to be within ± 15 per cent of the original standards.

It is a well known fact that prolonged starvation causes a marked diminution of the basal metabolism. It is also stated by some authors

13. Aub, J. C., and Du Bois, E. F.: Metabolism of Old Men, Arch. Int. Med. **19**:823 (May) 1917.

14. King, J. T., Jr., and Pearl, R.: Bull. Johns Hopkins Hosp. **32**:277 (Sept.) 1921. King, J. T., Jr.: Basal Metabolism, 1924.

15. Krogh, A.: Boston M. & S. J. **189**:313 (Aug. 30) 1923.

16. Sanborn: Basal Metabolism, 1922.

TABLE 3.—*Data for Normal Males Using Different Diets on the Previous Day*

PART 1

Case	Age	Date	Height in Cm.	Weight in Kg.	Surface Area Du Bois Height Weight Formula, Sq. Meters	Pulse Rate	Respiration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate: Du Bois Standards, per Cent	Basal Metabolic Rate: Harris and Benedict Standards, per Cent	Diet of Previous Day, Calories per Kg. of Body Weight
1	24	3/13	161.5	51.1	1.52	68	13	168	182	0.92	1,299	35.6	— 9.9	— 8.2	Usual
		3/14	.....	51.2	1.53	60	15	176	218	0.81	1,506	41.0	+ 3.8	+ 6.4	40.0
2	24	3/27	152.5	46.8	1.41	78	18	129	183	0.71	1,238	36.6	— 7.4	— 5.4	Usual
		3/28	.....	46.6	1.41	62	19	148	187	0.79	1,283	37.9	— 4.1	— 1.8	40.0
3	25	3/28	177.5	68.5	1.85	59	20	214	264	0.81	1,820	41.0	+ 3.8	+ 5.3	Usual
		3/29	.....	68.5	1.85	52	18	218	274	0.79	1,887	42.5	+ 7.6	+ 9.2	40.0
4	22	3/29	167.1	53.4	1.57	62	15	151	212	0.71	1,436	38.1	— 3.6	— 4.3	Usual
		3/30	.....	54.2	1.58	62	15	160	193	0.83	1,345	35.7	— 9.6	—10.3	40.0
5	22	4/ 5	158.0	48.3	1.47	62	14	148	191	0.77	1,312	37.2	— 5.8	— 5.3	Usual
		4/ 6	.....	48.7	1.47	59	15	164	199	0.82	1,379	39.1	— 1.0	— 0.4	40.0
6	23	4/ 6	162.7	56.0	1.60	54	19	158	213	0.74	1,448	37.7	— 4.6	— 3.1	Usual
		4/ 7	.....	56.0	1.60	56	19	193	227	0.85	1,590	41.4	+ 4.8	+ 6.3	40.0
7	28	4/ 7	162.2	50.0	1.52	69	14	166	214	0.78	1,481	40.6	+ 2.8	+ 7.6	Usual
		4/ 8	.....	50.2	1.52	64	12	170	196	0.87	1,382	37.9	— 4.1	+ 0.4	40.0
8	24	4/ 9	161.0	53.2	1.55	69	13	185	201	0.92	1,436	38.6	— 2.3	— 3.3	Usual
		4/10	.....	53.1	1.55	62	13	183	221	0.83	1,533	41.2	+ 4.3	+ 3.2	40.0
9	22	4/12	162.3	49.6	1.51	76	16	189	231	0.82	1,605	44.3	+12.2	+12.7	Usual
		4/13	.....	49.8	1.51	65	16	185	218	0.85	1,522	42.0	+ 6.3	+ 6.9	40.0
10	22	4/22	161.5	51.7	1.53	64	15	171	213	0.80	1,469	40.0	+ 1.3	+ 1.4	Usual
		4/23	.....	51.8	1.53	58	14	158	205	0.77	1,368	38.3	— 3.0	— 5.6	40.0
11	24	6/ 8	157.5	57.8	1.58	68	16	182	203	0.89	1,440	38.0	— 3.8	— 3.1	Usual
		6/10	.....	57.0	1.57	72	15	180	206	0.87	1,447	38.4	— 2.8	— 2.0	40.0
Average of usual diet				53.3	1.55	66	16	169	210	0.81	1,453	38.9	— 1.5	— 0.4	
Average of 40 calories per kilogram of body weight				53.3	1.55	61	16	176	213	0.82	1,476	39.5	0.0	+ 1.2	

PART 2

1	22	5/13	162.8	50.3	1.52	52	10	173	207	0.84	1,445	39.6	+ 0.3	+ 0.6	Usual
		5/14	.....	49.9	1.52	50	11	173	206	0.84	1,434	39.3	— 0.5	— 0.1	30.0
		5/15	.....	49.8	1.52	54	12	160	213	0.75	1,452	39.8	+ 0.8	+ 1.1	40.0
2	24	6/ 3	166.4	55.0	1.61	74	17	177	229	0.77	1,569	40.6	+ 2.8	+ 5.1	Usual
		6/ 4	.....	55.5	1.61	58	15	179	226	0.79	1,553	40.2	+ 1.8	+ 4.0	30.0
		6/ 5	.....	55.7	1.61	54	15	189	221	0.86	1,549	40.1	+ 1.5	+ 3.7	40.0
3	25	6/ 3	163.3	49.6	1.52	59	17	163	229	0.71	1,521	41.7	+ 5.6	+ 9.7	Usual
		6/ 4	.....	50.2	1.52	39	17	160	204	0.78	1,401	38.4	— 2.8	+ 1.1	30.0
		6/ 5	.....	50.7	1.53	57	17	165	198	0.83	1,375	37.7	— 4.5	— 0.8	40.0
4	24	6/10	155.7	53.2	1.51	58	22	157	220	0.71	1,479	41.2	+ 4.3	+ 4.5	Usual
		6/11	.....	53.8	1.52	42	18	165	205	0.80	1,412	38.7	— 2.0	— 0.2	30.0
		6/12	.....	53.8	1.52	70	17	173	198	0.87	1,390	38.1	— 3.5	— 1.7	40.0
5	23	6/17	167.2	47.6	1.52	70	17	146	188	0.78	1,295	35.5	—10.1	— 7.6	Usual
		6/18	.....	47.3	1.51	58	15	150	187	0.80	1,294	35.7	— 9.6	— 7.4	30.0
		6/19	.....	47.4	1.51	60	18	151	189	0.80	1,305	36.0	— 8.8	— 6.6	40.0
Average of usual diet				51.1	1.54	63	17	163	215	0.76	1,402	39.7	+ 0.5	+ 2.5	
Average of 30 calories				51.3	1.54	51	15	165	206	0.80	1,419	38.5	— 2.4	— 0.5	
Average of 40 calories				51.5	1.54	54	16	167	204	0.82	1,414	38.3	— 3.0	— 0.8	

The diet of 40 calories per kilogram when the patient weighed 50 Kg. consisted of boiled rice, 1,200 Gm.; eggs, two; potato, 100 Gm.; spinach, 100 Gm.; cabbage, 100 Gm.; beef, 100 Gm.; miso and soya equaling 2,110 calories, which contained protein, 86 Gm.; fat, 17 Gm., and carbohydrate, 391 Gm.

The diet of 30 calories per kilogram given to the same subject consisted of boiled rice, 900 Gm.; spinach, 100 Gm.; cabbage, 100 Gm.; potato, 100 Gm.; beef, 40 Gm.; miso and soya equaling 1,520 calories, which contained protein, 54 Gm.; fat, 2.7 Gm., and carbohydrate, 312 Gm.

TABLE 4.—*Data for Subjects Using Different Diets Successively for a Period*

Case	Age	Date	Height in Cm.	Weight in Kg.	Surface Area Du Bois Height-Weight Formula, Sq. Meters	Pulse Rate	Respiration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate: Du Bois Standards, per Cent	Basal Metabolic Rate: Harris and Benedict Standards, per Cent	Diet, Calories per Kg. of Body Weight	Days the Same Diet Was Used
1	23	5/17	160.7	56.4	1.59	66	18	170	200	0.85	1,404	36.8	— 6.9	— 5.8	Usual	
		5/18	.....	56.7	1.59	66	19	182	210	0.86	1,473	38.6	— 2.3	— 1.5	40.0	1
		5/23	.....	56.7	1.59	66	21	183	211	0.85	1,481	38.8	— 1.7	— 0.9	40.0	6
		5/25	.....	56.8	1.59	61	18	177	204	0.88	1,435	37.6	— 4.8	— 4.1	40.0	8
		5/28	.....	56.5	1.59	74	19	155	203	0.76	1,393	36.5	— 7.6	— 6.7	30.0	2
		5/29	.....	56.4	1.59	76	20	158	211	0.75	1,442	37.8	— 4.3	— 3.3	30.0	3
		5/30	.....	56.4	1.59	71	17	171	204	0.84	1,420	37.2	— 5.8	— 4.7	30.0	4
2	25	6/25	170.0	56.8	1.66	60	12	176	189	0.93	1,351	33.9	—14.1	—11.6	Usual	
		6/26	.....	56.3	1.65	58	12	163	183	0.89	1,295	32.7	—17.2	—14.9	40.0	1
		6/27	.....	56.3	1.65	54	17	176	189	0.92	1,338	33.8	—14.4	—12.1	40.0	2
		6/28	.....	56.3	1.65	48	13	161	179	0.90	1,275	32.2	—18.5	—16.2	40.0	3
		6/29	.....	55.2	1.64	59	15	178	195	0.91	1,385	35.2	—10.9	— 8.1	30.0	1
		6/30	.....	55.3	1.64	56	16	150	180	0.83	1,256	31.9	—19.2	—16.7	30.0	2
		7/ 1	.....	54.7	1.63	56	17	174	186	0.94	1,330	34.0	—13.9	—11.3	30.0	3
		7/ 2	.....	54.7	1.63	55	13	170	182	0.93	1,303	33.3	—15.7	—13.1	30.0	4
3	18	5/28	151.7	48.2	1.42	57	19	168	203	0.82	1,411	41.4	+ 1.0	+ 3.1	40.0	1
		5/29	.....	48.4	1.42	56	17	176	194	0.91	1,384	40.6	— 1.0	+ 1.1	40.0	2
		5/30	.....	48.6	1.43	56	21	163	186	0.85	1,311	38.2	— 6.8	— 4.4	40.0	3
		5/31	.....	49.2	1.43	56	22	179	192	0.93	1,338	39.0	— 4.9	— 3.0	40.0	4
		6/ 1	.....	49.2	1.43	54	20	178	191	0.93	1,369	39.9	— 2.7	— 0.8	30.0	1
		6/ 2	.....	48.7	1.43	56	19	171	197	0.87	1,390	40.5	— 1.2	+ 1.2	30.0	2
		6/ 5	.....	48.4	1.42	56	22	169	192	0.88	1,353	39.7	— 3.2	— 1.2	30.0	5
		6/ 7	.....	48.2	1.42	55	18	162	185	0.90	1,309	38.4	— 6.3	— 4.2	30.0	6
		6/ 9	.....	48.2	1.42	56	18	175	189	0.86	1,326	38.9	— 5.1	— 3.0	30.0	7
		6/ 6	.....	48.1	1.42	59	21	167	189	0.92	1,346	39.5	— 3.6	— 1.5	30.0	9

that a heavy meal on the previous day, especially in the evening, causes an increase. We made an investigation as to whether different diets and different amounts of nourishment have any influence on the basal metabolism. Table 3 gives a comparison of the basal metabolism of patients who observed usual dietary habits on the previous day and the same patients given 40 calories per kilogram of body weight per day. Similarly, table 4 gives a comparison of the basal metabolism of a patient on 30 calories and on 40 calories of the usual diet on the previous day. The influence of these moderate changes of diet on the basal metabolism is not significant. Table 5 also shows that a relatively prolonged use of different diets has almost no influence on the basal metabolism when the amount of the diet is not extraordinary.

From the foregoing results, the conclusion is that the basal metabolism of healthy Japanese is quite like that of Americans and Europeans and that no racial difference exists.

Benedict and Roth [17] found no significant difference in the metabolism of vegetarians and nonvegetarians. The food used in Japan is usually much richer in carbohydrate and poorer in fat than the Western style and the cooking also is quite different. In some cases we therefore prescribed Western cooking also on the day previous to the measurement and found no significant change in the basal metabolism. From these facts it is evident that the quality of the food has but little significance in the basal metabolism if enough essential foodstuff is given.

SUMMARY

In metabolism measurements on fifty-three normal Japanese, forty-two men and eleven women, ranging in age from 22 to 28 for the former and from 20 to 22 for the latter, the average height of the men was 161.9 cm. and of the women, 150.5 cm. The average weight for the former was 51.85 Kg. and for the latter, 50.0 Kg. The average surface area according to the Du Bois height-weight factors was 1.53 square meters, and according to the Harris and Benedict height-weight factors was also 1.53 square meters for the former and 1.43 and 1.47 square meters for the latter.

The vital capacity of the eleven women was somewhat low as compared with American data, being on the average 16.5 cc. per centimeter of height and 1.76 liters per square meter of surface area.

The blood pressure of the eleven women was normal.

The average pulse rate for the men was 64 beats per minute, with a minimum of 52 and a maximum of 80, and for women 70, with a minimum of 58 and a maximum of 90, values that are in accordance with American data considering that our subjects were all relatively young.

17. Benedict, F. G., and Roth, P.: J. Biol. Chem. **20**:231, 1915.

The respiration rate varied from 8 to 22 respirations per minute, averaging thirteen for men; for women it was from 8 to 21, averaging 15. When the subjects were breathing normally in the room, without mask, the average rate was 15 and 17, respectively.

The basal metabolism in 96 per cent of the cases showed deviations less than ± 15 per cent; in 87 per cent of the cases less than ± 10 per cent from the Harris and Benedict standards. The average deviation of the actually measured metabolism from the standards is —0.2 per cent for males and —3.9 per cent for females. A comparison of the heat production per square meter of body surface per hour with the Aub and Du Bois standards shows 98 per cent of the whole cases to be within ± 15 per cent, 89 per cent within ± 10 per cent of the standards. The average heat production in the males per square meter per hour was 38.7 calories, —2 per cent, and in the females 36.75 calories, —0.7 per cent of the standard. In view of the fact that Krogh, Benedict and others consider the present standards to be probably 4 or 5 per cent or more too high and that a comparison of the heat production in our cases with the standards of Du Bois as modified by Sanborn showed nearly the same percentage to be within ± 15 per cent of the original standards, it may be concluded that the basal metabolism of healthy Japanese is quite like that of Americans and Europeans and that no racial difference exists. Consequently we may have the convenience of applying the Western standards in the metabolic measurement of our subjects.

THE MECHANISM OF PAIN IN GASTRIC AND DUODENAL ULCERS

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INTRODUCTION

The genesis of pain arising from the stomach and intestine as the result of both functional and organic disorders has attracted much attention in recent years. Inflammation, muscle tension, acid irritation, edema, peritoneal irritation and perineural infiltration have all been ascribed their various rôles. The present work was undertaken with the hope that some aid might be obtained from a clearer understanding of the mechanism of pain in gastric and duodenal ulcers. It has naturally led into other fields at times, but attention has been focused chiefly on the benign peptic ulcer. One of the first problems encountered was that of the occurrence of ulcer and ulcer pain with achlorhydria.

LITERATURE

In the literature many allusions are found to ulcers with achlorhydria, but few of them are definite. For instance, in 1911, Gibson [1] stated that the free acidity in his ulcer cases varied from 0 to 0.18 per cent. Friedenwald,[2] in 1912, merely noted that hypochlorhydria or anacidity was observed in 188 of his 810 cases, or 23.2 per cent. Smithies [3] reported in 1913 that seven of his series of 131 cases had free acidities between 0 and 10. Crispin,[4] in 1916, reported eleven cases of duodenal ulcer in which the diagnosis was proved at operation, and in which there was achlorhydria. Eusterman [5] reported a case of gastric ulcer with anacidity in 1921. The following year Moynihan [6] found achlor-

* A dissertation submitted to the faculty of the Ogden Graduate School of Science in candidacy for the degree of doctor of philosophy.

* From the Seymour Coman Fellowship in the Department of Physiology of the University of Chicago and the Cook County Hospital.

1. Gibson, G. A.: Duodenal Ulcer Discussion, Edinburgh M. J. **6**:325 (April) 1911.

2. Friedenwald, Julius: A Clinical Study of a Thousand Cases of Ulcer of Stomach and Duodenum, Am. J. M. Sc. **144**:157, 1912.

3. Smithies, Frank: Gastric Ulcer Without Food Retention, Am. J. M. Sc. **145**:340-357, 1913.

4. Crispin: Duodenal Ulcer with Achlorhydria, Interstate M. J. **23**:890 (March) 1916.

5. Eusterman, G. B.: Ulcer Syndrome Despite Achlorhydria, M. Clin. N. Amer. **5**:40 (Sept.) 1921.

6. Moynihan, Berkeley: Some Problems on Gastric and Duodenal Ulcer, Brit. M. J. **1**:221 (Feb. 10) 1923.

hydria to be present in five of thirty-nine cases of gastric ulcer, and in four of seventy-one cases of duodenal ulcer. The same year, Bell [7] reported four cases of achlorhydria in twenty-seven cases of gastric ulcer, 14.8 per cent. In 1924, Heintz and Welker [8] reported three cases of gastric ulcer without free acidity. Udaonda [9] in Montevideo reported fifteen such cases in 1925. Eusterman [10] has recently stated that 4.5 per cent of gastric ulcers will show an anacidity. The number of reported cases, then, of peptic ulcer with achlorhydria is large, and its reported frequency in gastric and duodenal ulcers high, ranging from 4.5 to 23 per cent.

The explanation for the varying frequency of this condition in the different clinics is not apparent. There is, of course, the possibility that in some clinics patients with an indefinite abdominal distress are classified incorrectly as patients with ulcer, and also that in other clinics possible ulcers are excluded because of the apparent achlorhydria.

If we are to accept these reported cases, however, as bona fide cases of peptic ulcer with true achlorhydria, we must first examine them critically to determine whether they fulfil the requirements one has a right to expect such a case to fulfil; namely, is there adequate proof, first, that they are really simple benign peptic ulcers and, second, that true achlorhydria is present? The finding of a gastric ulcer at operation or at roentgen-ray examination is not adequate evidence of the character of the lesion, for the possibility of cancer and of syphilis must be excluded. The frequency of anacidity in both of these conditions is well known. Even the failure to find evidence of carcinoma microscopically is not incontrovertible evidence of the benign nature of the lesion, for Moynihan [6] has reported two such cases in which the patients died from carcinoma metastases three and five years later. The finding of a definite duodenal ulcer at operation, however, as Crispin reported, must be considered as more adequate evidence of ulcer.

But what are we to consider as adequate evidence of achlorhydria? It is not the intent of this article to enter into a detailed discussion of the mechanism of gastric secretion. This has been well worked out by Ivy, Lim and McCarthy.[11] Dobson [12] has grouped the achlorhydrias

7. Bell, J. R.: Gastric Ulcer and Achlorhydria, Arch. Int. Med. **32**:663 (Nov.) 1923.

8. Heintz, E. L., and Welker, W. H.: Acidity Curves in Gastric, Duodenal and Mixed Ulcers, Ann. Clin. Med. **3**:371 (Nov.) 1924.

9. Udaonda: Functional Achylia, An. de Fac. de med., Montevideo, **9**:799 (Sept.) 1924.

10. Eusterman: The Newer Aspects of Gastric Carcinoma, Radiology **6**:409-415 (May) 1926.

11. Ivy, A. C.; Lim, R. K., and McCarthy, J. E.: Contributions to the Physiology of Gastric Secretion, Quart. J. Exper. Physiol. **15**:13-68 (March) 1925.

12. Dobson, H. V.: Effect of Histamine on Gastric Secretion, J. A. M. A. **84**:158 (Jan. 17) 1925.

on the basis of their response to histamine. The question at present is to determine the reliability of the clinical tests that are generally considered as adequate evidence of achlorhydria.

With a single exception, which will be mentioned later, all the cases cited in the literature as instances of ulcer with achlorhydria are based on the failure to find free acid either in an ordinary Ewald test meal or Boas test meal removed at the end of an hour, or in a fractional Ewald or Boas test meal in which samples are removed and titrated every fifteen minutes. The first table shows an illustration of the fallacy involved in assuming that anacidity in an Ewald test meal is adequate evidence of true achlorhydria. This is a list of eighteen persons having either a proved or a probable peptic ulcer, who had an absence of free acid in one Ewald test meal but free acid at another

TABLE 1.—*Cases Illustrating Wide Variations in Gastric Acidities as Revealed by Ewald Test Meals*

Case	Free Acidity*	Total Acidity
1	0-5	52-23
2	0-7	17-20
3	0-24	40-60
4	0-29 †	34-68 †
5	0-25	25-68
6	0-28	25-35
7	0-45-80	20-60-92
8	0-43-45	11-60-54
9	0-15-18	30-50-42
10	0-15-18-59	8-35-35-83
11	0-10-43-45	42-29-48-60
12	0- 8-16-18-20-48	14-22-36-48-48-70
13	0-trace-11-19-35	20-30-39-41-80
14	0-0-11	28-34-21
15	0-0-25	52-78-79
16	0-0-14-70	35-43-50-88
17	0-0-24-40-40	8-13-70-54-63

* The free acid values were arbitrarily arranged to increase from left to right.
† Control aspiration.

time. These eighteen were selected from a series of 1,469 cases recently reviewed at the Presbyterian Hospital. Four of them showed no free acid in two Ewald test meals. Furthermore, the total acidity in four was less than 15. This is of interest because Kelling,[13] Schütz [14] and Girardi [15] have stated that a total acidity of less than 15 or 20 may be considered as evidence of complete achlorhydria. Attention is also called to the wide range in the free acidity values, from 0 to 70.

The second table shows the fallacy involved in assuming that anacidity as revealed by a fractional test meal is adequate evidence of

13. Kelling, G.: Statistiches über der Salzsäuremangel im Magen, Arch. f. Verdauungskr. **15**:568, 1909.
14. Schütz, E.: "Uber Anazidität," Arch. f. Verdauungskr. **30**:233 (Jan.) 1921.
15. Girardi: False Achylia Gastrica, Gazz. d. osp. **4**:412, 1924.

achlorhydria. Here again it is noted that the maximum total acidity in two cases is less than 15 and in another case is less than 20.

Hence, the reported cases of peptic ulcer with achlorhydria have to be considered as unproved because the evidence presented of true and complete achlorhydria is inadequate.

TABLE 2.—*Cases Illustrating Wide Variations in Gastric Acidities as Revealed by Fractional and Ewald Test Meals* *

	Fractional Meal Maximum Acidity		Ewald Meal	
	Free	Total	Free	Total
Chronic ulcer of body of stomach: Page 106, case 6	0	17	41	70
case 100	0	33	28	44
Hour-glass stomach: Page 109, case 242	0	26	38	52
Visceroptosis: Page 109, case 200	0	6	19	36
Carcinoma of stomach: Page 119, case 180	0	53	32	57
Cirrhosis of the liver: Page 130, case 195	0	12	29	49

* These cases are taken from Donald Hunter's "Study of Fractional Test Meal," Quart. J. Med. **16**: 95-134 (Jan.) 1923.

INVESTIGATIONS AT THE PRESBYTERIAN HOSPITAL

In an effort to find more conclusive data on the subject, the files at the Presbyterian Hospital were searched for such cases recently, with the thought that perhaps it might be possible to find there proved cases of peptic ulcer in which repeated gastric analyses had failed to show free acid at any time. The Presbyterian Hospital was chosen because at no other hospital, so far as I know, has there been such

TABLE 3.—*Cases of Proved or Probable Peptic Ulcer Showing No Evidence of Free Hydrochloric Acid (Presbyterian Hospital Series)*

	Ewald Acidities	
Case	Free	Total
1	0	32
2	0	16
3	0	12
4	0 *	23 *
5	0-0-0 †	8-12-62 †
6	0-0 ‡	110-20 ‡
7	0-0-0-0	10-18-20-28

* Motor meal.
† Riegel meal.
‡ Fractional meal, Mayo Clinic.

extensive use of Sippy's therapeutic aspiration, which is the aspiration made at the height of distress and which will give, on the average, a higher acid value than the Ewald test meal. The study included 1,004 proved ulcers and 465 probable ulcers. The third table shows a list of all of the cases found which failed to show free acid at any time. The first four may be discarded at once because the sole evidence of achlorhydria is that of a single test meal. The fifth case may be disregarded

for three reasons: first, because a definite diagnosis of ulcer was not made and the symptoms were not typical ulcer symptoms but consisted chiefly of morning nausea and loss of appetite; second, because there was no definite evidence of ulcer, and, third, because the patient had previously had a gastro-enterostomy and a gastric resection which altered the gastric chemistry. It is known that an "excessive amount of free hydrochloric acid" was present prior to the third operation.[16] The sixth and seventh cases cannot be excluded so easily, and it is necessary to consider them in detail.

A brief resumé of the sixth case is as follows:

L. J. P., a man, aged 53, on Oct. 8, 1914, entered the Presbyterian Hospital, in the service of Dr. B. W. Sippy, complaining of epigastric distress of seventeen years' duration—a fair ulcer story until the last year or two. The Ewald meal was 0-10. The motor meal was 0-14.

On October 9, a therapeutic aspiration was performed for distress. Free hydrochloric acid was 0; total, 70.

On October 12, a motor meal test was 0.185; long bacilli and lactic acid were present. Sixteen other aspirations at various intervals after eating during the following week failed to reveal free hydrochloric acid at any time, making twenty aspirations in all without free acid.

On October 19, a laparotomy was performed by Dr. Dean Lewis. "The stomach wall was found edematous with a ring-shaped thickening of soft consistency about the pylorus." The diagnosis was syphilis of the stomach with obstruction. A posterior gastro-enterostomy was done.

On November 3, the diagnosis at discharge was pyloric obstruction and ulcer of the stomach.

In August, 1920, he consulted the Mayo Clinic for stomach trouble. A fractional test meal showed a maximum free acidity of 0; total acidity, 20. Roentgen-ray examination revealed an extensive lesion of the stomach, gastro-enterostomy free. The stomach was reported to be unusually small and shrunken. A blood Wassermann test was strongly positive; a spinal fluid test was negative. There was a history of a primary syphilitic lesion in 1895. The diagnosis was posterior sclerosis, probably arteriosclerosis, and gastric syphilis.

In August, 1921, the patient died. The diagnosis was arteriosclerosis, cerebral type, and syphilis of the stomach. No necropsy was performed.

In spite of the rarity of gastric syphilis, apparently there is sufficient evidence to justify this diagnosis, and hence it must be excluded.

A brief resumé of the seventh case follows:

O. F., a man, aged 56, on Dec. 4, 1913, entered the Presbyterian Hospital, in the service of Dr. Dean Lewis, complaining of constipation and epigastric pain of a year's duration; the distress was definitely not typical ulcer distress.

On December 5, an Ewald test meal showed free hydrochloric acid, 0; total hydrochloric acid, 28. A motor meal showed free hydrochloric acid, 0.

On December 6, an Ewald test meal showed free hydrochloric acid, 0; total, 20. A motor meal showed free hydrochloric acid, 0.

On December 9, a therapeutic aspiration of 60 cc. was performed for distress. Free hydrochloric acid was 0; total, 33. No relief was felt.

On December 12, a laparotomy was performed by Dr. Lewis. There was an old scar from a healed gastric ulcer near the pylorus and a duodenal ulcer with a definite crater. There was no evidence of malignancy. A gastro-enterostomy was done.

On December 27, an Ewald test meal showed free hydrochloric acid, 0; total, 10; lactic, 0; a motor meal, free, 0; total, 10.

16. Davis, T. I.: Personal communication to the author.

On December 29, an Ewald test meal showed free hydrochloric acid, 0; total, 18.

On January 17, a therapeutic aspiration of 200 cc. was performed for severe distress. Free hydrochloric acid was 0; total, 17. No relief was felt.

On February 14, the patient committed suicide because of failure to obtain relief from distress. Necropsy revealed a healed duodenal ulcer. Sections through the base of the scar revealed no evidence of malignancy.

Several points are of great interest. The diagnosis of duodenal ulcer was proved by laparotomy and by the finding of the scar of the healed ulcer at necropsy. No free acid was present in any one of the nine gastric analyses. Perhaps this cannot be considered as true and complete achlorhydria because the total acidity was twice more than 15 and once more than 20, and there is no record of a histamine test. Nevertheless, it must be considered as a practical achlorhydria. Certainly there is more evidence of achlorhydria here than is reported to have been present in any of the cases cited in the literature. But there is another important thing to be noted here—the man committed suicide because of failure to obtain relief from a distress which continued after the ulcer had healed. In other words, the only distress of which he complained, the distress for which he entered the hospital and underwent an operation, continued unrelieved after the ulcer had healed, and was severe enough to cause him to commit suicide. No explanation for the distress was found at necropsy.

Probably this case should be accepted as one of duodenal ulcer without free hydrochloric acid. However, if we are to accept it as a case of ulcer distress without free acid, we must take the stand that a healed ulcer can cause pain. Dr. Eusterman of the Mayo Clinic has called my attention recently to a case of theirs in which typical ulcer pain was present, but in which at necropsy a healed duodenal ulcer was the only lesion found. Eusterman[17] also states that patients with pyloroplasties will often have a recurrence of ulcer symptoms without an ulcer being demonstrable at reoperation. Clinical experience on the whole, however, teaches that painful ulcers are active ulcers, and that healed ulcers are painless. At present, this seems to be the most rational view, and hence one hesitates to conclude that the distress in this particular case was in any way related to the ulcer, either before it healed or after it healed. At the same time, it must be admitted that the question is an open one and calls for further investigation.

Hence of this series of 1,004 proved ulcers and 465 probable ulcers, as is shown in table 4, all four of the probable or suspected ulcers with achlorhydria must be disregarded because of the lack of evidence both as regards the presence of ulcer and the presence of achlorhydria; one fairly well proved duodenal ulcer must be disregarded because of the

17. Eusterman, G. B.: Personal communication to the author from the Mayo Clinic.

lack of sufficient evidence as regards the achlorhydria; one gastric ulcer must be reclassified as a probable syphilitic lesion, and one duodenal ulcer must be accepted as a case of duodenal ulcer without free acid and apparently without pain directly attributable to the ulcer. In other words, there is no incidence of achlorhydria in the proved gastric ulcers, and of only 0.12 per cent in the proved duodenal ulcers—the one case.

INVESTIGATIONS AT THE MAYO CLINIC

Because of the marked difference between these observations and those in the literature, it seemed wise to see what definite evidence could be obtained on the subject at the Mayo Clinic. Bueerman [18] has been reviewing their records recently and is preparing a report. In his notes, which he allowed me to see, three cases particularly are of interest. The first patient was a person with roentgenologic evidence of duodenal ulcer. Three fractional test meals revealed an entire absence of free acid and a total of not over 20, but a free acid of 14 was obtained in

TABLE 4.—*Summary of Cases Reviewed at Presbyterian Hospital*

	Proved Ulcers			Probable Ulcers
	Gastric	Duodenal	Total	
Number of cases	110	894	1,004	465
Free acid present	109	892	1,001	461
Possible achlorhydrias	1	2	3	4
Syphilis	1	..	1	..
Inadequate evidence of achlorhydria	..	1	1	4
Ulcer with achlorhydria	0	1	1	0
Incidence		0.12%	0.1%	

response to the subcutaneous injection of a quarter of a milligram of histamine hydrochloride. This shows the fallacy of accepting even three fractional test meals as conclusive evidence of complete achlorhydria. The second is a patient with a good ulcer history of ten years' duration and roentgenologic evidence of a duodenal lesion. Two fractional test meals revealed an absence of free acid and total acidities of 26 and 30. The subcutaneous injection of 0.5 mg. of histamine chloride failed to produce any free acid, but a total acidity of 40 was noted. Aspiration is said to have been performed in this case at the time of distress without the finding of free acid, but the figures as regards the amount of gastric content obtained and its total acidity are not available. This must be regarded as a suggestive case, but one hesitates to accept it as conclusive until the figures are recorded and its further course is followed. The third case is one with a rather typical ulcer history of ten months' duration. A penetrating duodenal ulcer was found at operation, and the symptoms did not reappear after gastro-enterostomy.

18. Bueerman, W. H.: Personal communication to the author. The Surgical Significance of Duodenal Ulcer with Achlorhydria, to be published.

Two fractional test meals before gastro-enterostomy and four at various times later failed to reveal any evidence of free acid. A year later, the patient returned with a well developed pernicious anemia. An examination of the gastric content at the time of distress was not made. This is, perhaps, a better case than the preceding one, but one hesitates to accept it also without knowing more of the details, such as the time of the appearance of the pernicious anemia and the character of the gastric content at the time of distress.

Of these three cases, then, the first was shown not to be a true achlorhydria by means of the histamine test; the other two are very suggestive and must be considered as cases of duodenal ulcer with possibly complete achlorhydria.

ADDITIONAL CASES

There has recently been a patient at the Cook County Hospital who must be considered in this connection.

M. F., a man, aged 56, in September 1923, consulted the Pelton Clinic,[19] Elgin, Ill., for "gnawing, burning" epigastric distress of four or five years' duration; it was worse in the winter and practically absent in the summer, coming on one-half to three hours after eating and lasting continuously for an hour or two, when it would disappear spontaneously or be relieved by eating or by vomiting. A drachm (4 Gm.) of soda gave relief for only half an hour or so. An Ewald test meal showed free acid, 0; total, 11. Boas-Opler bacilli were absent. Milk coagulation was negative in all the tubes. A laparotomy revealed a diseased gallbladder with extensive adhesions and an old ulcer scar on the anterior surface of the duodenum. A cholecystectomy and a posterior gastro-enterostomy were done.

On Dec. 2, 1925, the patient entered Cook County Hospital, complaining of severe, cramplike pain about the navel, different from his old pain, and of the vomiting of a quart of blood twelve hours previously. A therapeutic aspiration of 11 cc. for severe pain was performed. Free acid was 0; total, 39. No relief was obtained from the aspiration. The distress subsided forty-eight hours later.

On December 3, an Ewald test meal revealed free acid, 0; total, 40. Blood was present. A motor meal showed free acid, 0; total, 36. Blood was present.

On Feb. 2, 1926, an Ewald test meal showed free acid was 0; total, 18.

On February 19, 1 mg. of histamine hydrochloride was given subcutaneously. Free acid was 0; total, 11.

On April 7, 1.5 mg. of histamine hydrochloride was given subcutaneously. Free acid was 0; total, 14.

This case must also be considered as suggestive, but it cannot be accepted as conclusive, because the evidence of true achlorhydria prior to the gastro-enterostomy is inadequate, and the nature of the lesion following gastro-enterostomy was not conclusively determined.

There seems to be reported in the literature only one case of ulcer with no free acid in a therapeutic aspiration at the time of distress. This is reported separately by Eusterman [5] and by Hardt.[20] Adequate free

19. Pelton, O. L., Jr.: Personal communication to the author from the Pelton Clinic, Elgin, Ill.

20. Hardt, L. L. J.: Studies of the Cause of Pain in Gastric and Duodenal Ulcers: II. Peristalsis as Direct Cause of Pain in Gastric Ulcers with Achylia and in Duodenal Ulcers, Arch. Int. Med. **29**:684 (May) 1922.

acidity was present in this case prior to gastro-enterostomy for a duodenal ulcer. Later, the patient returned with a large penetrating gastric ulcer. At this time, according to Eusterman, aspirations made during his pain averaged a total acidity of 6, no free acid, and an average amount of 50 cc., consisting almost entirely of a bile tinged fluid and some mucus.

Ryle [21] reports another case of recurrence after gastro-enterostomy in which pain is said to have occurred in the absence of free acidity. There is no mention of therapeutic aspirations made at the time of distress, and one must infer that the statement is based on test meal observations only.

CONCLUSIONS

It is difficult to draw many definite conclusions on this subject at present, but one may summarize the situation as follows:

1. Repeated Ewald or fractional test meals cannot be accepted as giving conclusive evidence of achlorhydria even when the total acidity is less than 15.

2. The previously reported cases of duodenal or gastric ulcer with achlorhydria cannot be accepted as being satisfactorily proved as yet.

3. In a case of duodenal ulcer with no free acid in nine Ewald test meals, motor meals and therapeutic aspirations reported, there is evidence that the pain cannot be attributed to the ulcer with certainty, for it continued after the ulcer had healed. This is the only case of definite achlorhydria found in a review of 1,004 proved gastric and duodenal ulcers at the Presbyterian Hospital.

4. An absence of free acid both in test meals and in therapeutic aspirations made at the time of distress attributable to a benign gastric or duodenal ulcer has been reported definitely in only one case, that of a perforated gastric ulcer.

5. Because of the practical importance of this question in the genesis, chronicity and pain of ulcer, it is hoped that all those who are in a position to manage and observe patients with ulcer will prove any achylias which they may encounter in proved ulcers by repeated test meals, by injections of histamine and by repeated therapeutic aspirations and titrations made at the time of distress attributable to the ulcer.

21. Ryle, J. A.: Gastric Function in Health and Disease, London, Oxford Univ. Press, 1926, p. 64.

RENAL DWARFISM

REPORT OF A CASE *

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The association of chronic nephritis with bone changes in adolescents is apparently so uncommon as to have escaped general attention. In 1883, Lucas [1] reported several cases of late rickets associated with albuminuria. Among these was one case of chronic nephritis associated with rachitic changes in the bones. The case was, however, not fully studied or followed. Apparently he did not recognize the case as peculiarly one of chronic nephritis in which rickets occurred. In 1911-1912, Fletcher, Miller and Parsons [2] described instances of the association of chronic interstitial nephritis with bone changes, but it was not until 1920 that Barber compiled a series of ten cases in adolescents and called the syndrome "renal dwarfism." [3] This aroused considerable discussion in the British literature, but until recently the condition has failed to attract any appreciable notice in the American journals.[4]

This disease as described by the British authors is characterized by an insidious onset in early puberty of mild headache, drowsiness, albuminuria, fixation of the specific gravity of the urine at a low level, polyuria, anemia, dwarfism unassociated with any mental changes, bone deformities of a rachitic nature, failure of development of the secondary sexual characteristics, slight cardiovascular change, and inevitable termination in uremia sometime in the second decade of life. The symptoms are thus largely those of chronic nephritis, plus bone changes simulating rickets.

Only seven cases that were examined at necropsy have been recorded in the literature.[5] The pathologic picture they have presented is fairly characteristic. As a rule the cardiovascular system is normal. The kidneys show a chronic interstitial nephritis. The bones have apparently

* From the medical clinic, Johns Hopkins University Medical Department.

1. Lucas, R. C.: Lancet, 1883, pp. 79, 993.

2. Fletcher, H. M.: Proc. Roy. Soc. Med. (Sect. Dis. Child.) **4**:95, 1911. Miller, R.: Proc. Roy. Soc. Med. (Sect. Dis. Child.) **5**:38, 1911. Parsons, L.: Brit. M. J. **2**:481, 1911. Miller, R., and Parsons, L.: Brit. J. Child. Dis. **9**:289, 1912.

3. Barber, Hugh: Brit. M. J. **2**:1204, 1913; Quart. J. Med. **14**:205, 1920; Lancet **1**:18 (Jan. 3) 1920; Guy's Hosp. Rep. **71**:62 (Jan.) 1922.

4. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, N.: Am. J. Dis. Child. **23**:91 (Feb.) 1922. Smith and Walsh: To be published.

5. Barber (footnote 3). Paterson, D. H.: Proc. Roy. Soc. Med. (Sect. Dis. Child.) **13**:107 (June) 1920; Brit. J. Child. Dis. **18**:186 (Oct.-Dec.) 1921; Lancet **1**:944 (May 13) 1922. Naish, A. E.: Brit. J. Child. Dis. **9**:337, 1912.

not been studied by the pathologists except by Patterson,[6] who, however, differentiates the changes that occur from those of rickets and considers the changes as due to some undetermined fault in the calcium metabolism.

The condition is apparently relatively uncommon. In the fourteen cases so far reported,[7] the age of onset varied from 7 to 17 years, with an average age at onset of 12½ years. The age at death varied from 9½ to 20, with an average of 14 years. The average duration of symptoms was a trifle over one and one-half years, varying from six months to six years. Barber in his series [3] gives two cases of chronic interstitial nephritis in which infantilism was present without bone deformities. There is an allied group of cases in which the symptoms of nephritis and the bone changes were present at birth or shortly after.[8] All the latter patients died before the age of 10.

The following case of renal dwarfism is of interest not only because it offers such a typical example of renal dwarfism but also because it gave us the opportunity to make certain chemical studies of the patient's blood over a long period of time.

REPORT OF CASE

E. C., a girl, aged 15, was admitted to the Johns Hopkins Hospital, April 6, 1925, complaining of drowsiness and anorexia. The patient was the youngest of ten children, all of whom were living and well. There was no history of tuberculosis, syphilis or renal disease in the family. All the other members of the family were fairly tall. The patient had pertussis at 8 months, smallpox at 5 years, measles at 8 years, influenza at 9, typhoid fever at 11, and mumps at 13. There was no history to suggest scarlatina, diphtheria or tonsillitis. She was never strong but seemed to develop normally till after the attack of typhoid fever at 11; since then a distinct retardation of physical growth had been noticed. Mentally the child had continued to develop normally, and was unusually bright in school. Her catamenia had not yet begun.

The onset of the present illness was dated definitely from the age of 12, two and one-half years before admission. At that time there had been a gradual onset of fatigability, lack of energy and drowsiness. She became so drowsy she would fall asleep while eating. She was taken to a physician because her parents believed she might be having sleeping sickness. It is reported that albumin was found in the urine at that time. In November, 1922, she was admitted to the Montgomery General Hospital, Montgomery, W. Va. The urine at that time showed a light cloud of albumin, an average specific gravity of 1.006, and an occasional granular cast. The blood pressure was 110 systolic, 70 diastolic. The phthalein output was 11 per cent and the nonprotein nitrogen 74 mg. (table 1). She was in the hospital seven weeks and was discharged improved. During the succeeding two and one-half years she had been in and out of the Montgomery Hospital five times. Soon after the first discharge her drowsiness returned, and

6. Patterson (footnote 5, second reference).

7. Fletcher; Miller; Parsons; Miller and Parsons (footnote 2). Barber (footnote 3). Patterson (footnote 5, second reference). Naish (footnote 5, fifth reference). Feiling, A., and Holyoak, W. L.: Proc. Roy. Soc. Med. (Clin. Sect.) **15**:1, 1922.

8. Fletcher (footnote 2, first reference). Paterson (footnote 5, second reference).

with it frontal headaches, nausea and vomiting. From this time on her height and weight apparently remained almost stationary. Two years before admission to the Johns Hopkins Hospital there is said to have been a sudden onset of knock-knee, which had become progressively worse but had not interfered with walking. For a year and a half she had had palpitation and dyspnea on exertion, with puffiness of the eyelids in the morning and slight swelling of the feet and ankles at night. For over a year she had had almost constant thirst with polyuria and nycturia. For a month previous to admission to this hospital she had had complete anorexia, with dull pain in the right upper quadrant following meals.

On physical examination, the temperature was 99, the pulse 100, the respirations 20. The height was 4 feet 7½ inches. The weight was 73¼ pounds (33.2 Kg.). The blood pressure was 110 systolic, 60 diastolic. The patient was a very

TABLE 1.—*Blood Examination at Montgomery General Hospital* *

	Nov., 1922	Feb., 1924	March 4, 1924	March 10, 1924	March 14, 1924	March 19, 1924	Jan. 26, 1925
Nonprotein nitrogen	74	98	110	118	72	120	161
Urea nitrogen	52	72.6	82	93.3	58	96	...
Creatinine	..	2.5	...	4.54	3.67	3.14	...

* All figures in the tables are in terms of milligrams per hundred cubic centimeters of whole blood. The figures in this table were lent by W. J. Laird, Jr., M.D., Montgomery, W. Va.

TABLE 2.—*Blood Examination at Johns Hopkins Hospital*

	April 7, 1925	April 11, 1925	April 13, 1925	April 17, 1925	April 23, 1925	April 30, 1925	May 9, 1925	May 11, 1925	May 13, 1925
Nonprotein nitrogen	100	95.3	...	.....	113.2	141	176	....	244
Nonprotein nitrogen of plasma	.....	....	...	158	.....	.....	.....	....	.....
Creatinine	7.3	....	...	.....	.....	.....	.....	....	.....
Uric acid	5.3	....	...	.....	.....	.....	.....	....	.....
Carbon dioxide capacity	30.5	....	...	33.2	32.6	.....	21	18.9	24.2
Hydrogen ion concentration of blood	.....	....	...	.....	.....	.....	7.32	6.98	.....
Phosphates	.....	....	9.2	.....	.....	9.1	.....	....	9.5
Total calcium	.....	....	5.9	.....	.....	4.6	.....	....	4.6
Free calcium	.....	....	...	.....	.....	3.8	.....	....	.....
Total protein	.....	....	...	7.32	.....	.....	.....	....	.....
Albumin	.....	....	...	4.36	.....	.....	.....	....	.....
Globulin (including fibrin)	.....	....	...	2.96	.....	.....	.....	....	.....
Fibrinogen	.....	....	...	0.562	.....	.....	.....	....	.....
Albumin-globulin ratio	.....	....	...	60/40	.....	.....	.....	....	.....
Sodium chloride	.....	....	...	593	.....	.....	.....	....	.....
Sodium	....	....	...	.....	.....	.....	.....	....	0.290
Sugar	.....	....	...	.....	0.099	.....	.....	....	.....

intelligent and cooperative child, but rather drowsy. She was well nourished but greatly underdeveloped. The breasts were small, and there was an absence of secondary sexual characteristics. There was a puffiness about the eyes and a pasty pallor to the face. There was a uriniferous odor to the breath. The skin was coarse and dry; there was no edema. There was marked genu valgum (fig. 1), beading of the costochondral junctions, and a very slight thickening of the epiphyses at the wrists. The ophthalmologic examination showed a normal fundus. The heart was not enlarged to percussion, measuring 7 cm. to the left of the mid-sternal line in the fourth interspace and 4 cm. to the right in the third interspace. No endocardial murmurs were heard. The abdomen was entirely negative; the liver, spleen and kidneys were not felt. The blood showed a red cell count of 2,500,000; hemoglobin, 41 per cent; white cell count, 12,400. The differential count was normal. The urine was pale and clear, with a specific gravity varying

from 1.005 to 1.010 and albumin varying from 1 to 2 Gm. per liter (Esbach). Twenty microscopic examinations showed large numbers of leukocytes but no red cells and no casts. The guaiac test was negative in all specimens examined. The figures on certain of the chemical constituents of the blood are given in table 2. Specimens of urine collected at two hour intervals showed a fixation of the specific gravity at from 1.008 to 1.009. The Wassermann reaction was negative. The roentgen ray showed the heart to be normal in size, and showed a marked retarda-

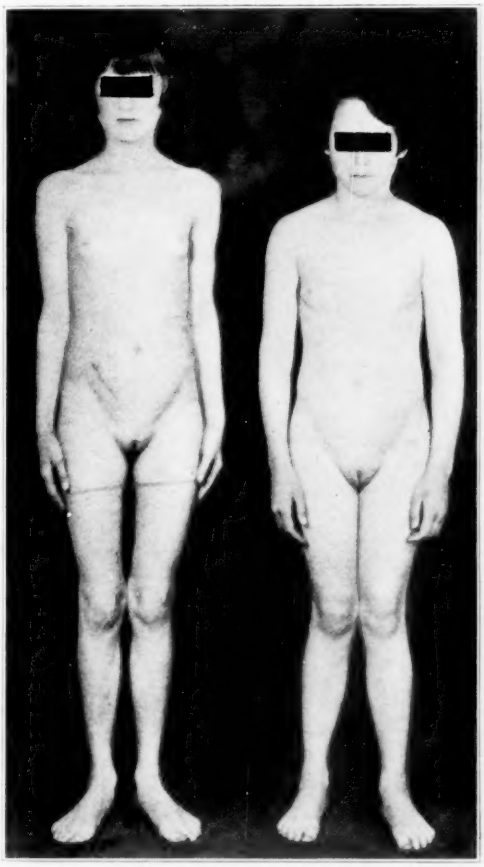

Fig. 1.—Left, twelve year old diabetic girl; right, patient described here.

tion of development of the epiphyses, especially at the wrist (fig. 2). The electrocardiographic report was normal except that the P-R interval was a little long for the age. The blood pressure remained fairly constantly at 120 systolic, 80 diastolic, until the last few days of life, when it became very irregular, ranging from 90 systolic, 20 diastolic, to 150 systolic, 80 diastolic, in a single day. The temperature remained normal except for a terminal rise due to a terminal bronchopneumonia. The pulse remained constantly between 90 and 100.

Her course in the hospital was progressively downward. For the first few weeks she seemed to improve. She became lively and vivacious, playing freely with the girl in the next bed. Contrary to the clinical improvement, however, the nonprotein nitrogen of the blood remained in the neighborhood of 100 mg. She suffered from occasional nausea and on rare occasions she vomited. For one period she complained of transient diplopia. She developed a peculiar brownish pigmentation of the face. May 7, she began to show a drowsiness from which at times it was difficult to arouse her. By the next day it was noticed that she was becoming more dyspneic. She sank rapidly and a few days later was in coma with great air hunger. Alkalis were administered freely, which seemed to lessen slightly the coma and made the breathing much less labored. There was slight

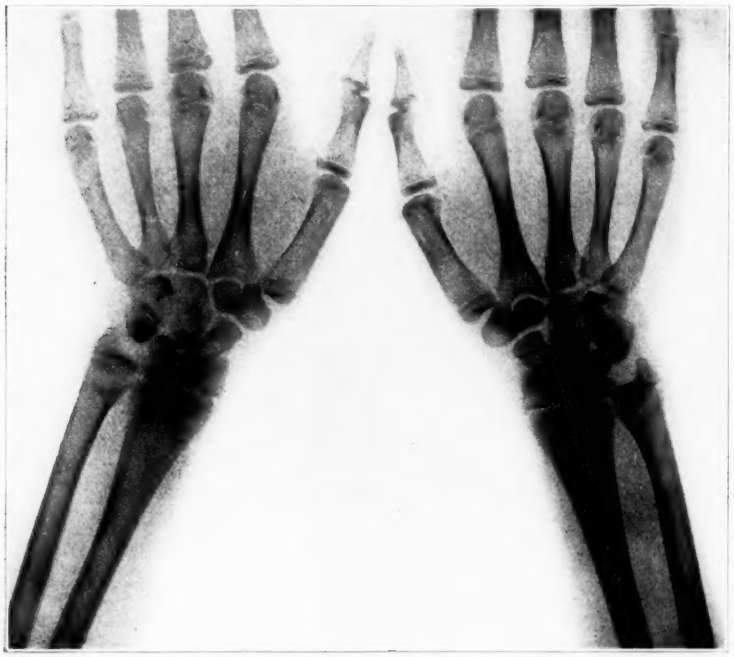

Fig. 2.—Wrists of patient.

bleeding from the nose and mouth. The pulse became irregular and the respirations feeble. The evening of May 14, 1925, she died, apparently of respiratory failure.

Necropsy was performed by Dr. A. R. Rich. The anatomic diagnosis was renal dwarfism; peculiar nephritis; thickening of the bladder mucosa and kidney pelvis; early lobular pneumonia; hyperplastic bone marrow; diphtheric laryngitis and rickets.

Briefly the pathologic report was as follows:

Grossly the heart and blood vessels showed nothing abnormal, but there was diffuse, very fine scarring of the myocardium on microscopic examination.

The bony and renal changes were the most striking. Grossly the bones showed an irregular line of ossification with small yellowish opacities beneath this line. The bone was apparently softer than normal because it was cut more easily than is usual. On microscopic examination, the line of ossification in the ribs was found

to be very irregular and in places between the cartilage and the bone there were broad zones of loose connective tissue in which islands of osteoid tissue were embedded.

The kidneys were extraordinary in appearance. They were both distorted pieces of tissue which externally hardly resembled kidneys. The left kidney weighed 40 and the right only 35 Gm. The capsules stripped with difficulty. The surfaces of the kidneys were rough and scarred. On section the kidney architecture was found to be almost unrecognizable. The cortex was only 3 mm. in thickness. The organs were very dense and firm and were cut with much more

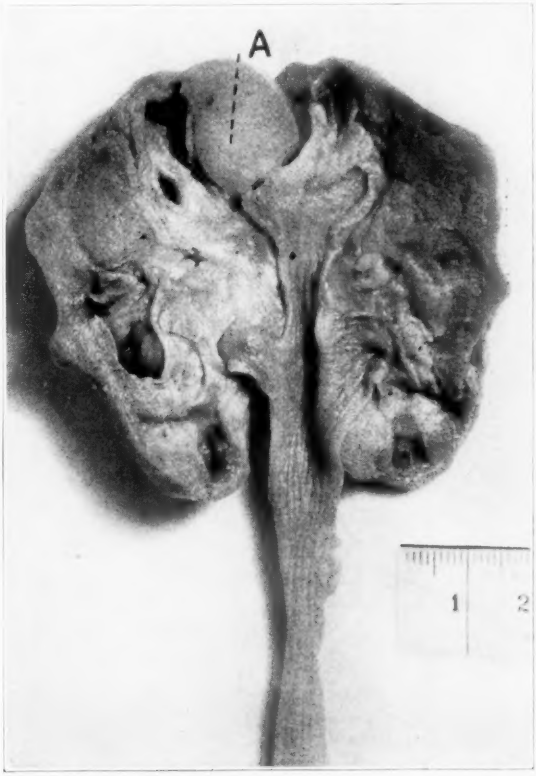

Fig. 3.—Left kidney, showing scarring, obliteration of cortex, and *A*, nodule of compensatory hypertrophy; actual size, with centimeter rule.

difficulty than normal kidneys. There were no hemorrhages to be seen in the kidney structure. The blood vessels were prominent but not especially sclerotic. The ureteral lining near the pelvis was distinctly thickened but no fresh inflammatory reaction was seen in the pelvis or ureter. The bladder wall was not thickened but the bladder lining presented a peculiar appearance. It showed no injection of the blood vessels nor any sign of recent inflammation but it was thickened and thrown into translucent whitish plaques having narrow crevices

between them. The plaques were wrinkled. The ureteral orifices were patent. Microscopically the kidneys showed the following picture: A cross section of the entire kidney fitted easily beneath the usual oblong cover slip. There was a complete distortion of the normal kidney architecture. There were numerous old scars throughout the section in which the remnants of tubules and partly or completely obliterated glomeruli and blood vessels were embedded. In these areas collections of small lymphocytes were prominent and the arterioles were numerous because of their being brought together by collapse of the intervening parenchyma. The scars contained many dilated capillaries and venules and in some places there were cavernous telangiectatic dilatations of the capillaries. In

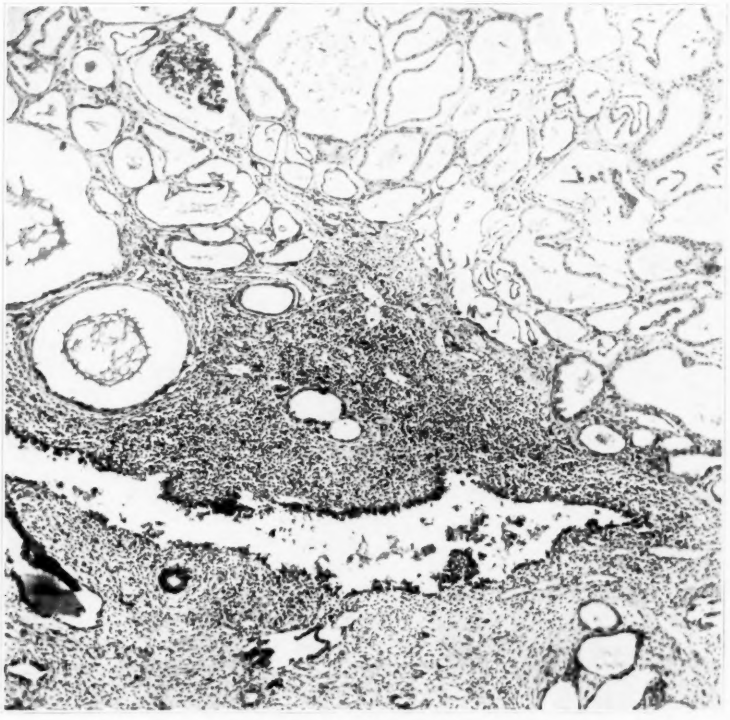

Fig. 4.—Pelvis of kidney with round cell infiltration.

the regions between these scars there were everywhere enormously dilated tubules lined with low cuboidal cells or, often, quite flattened remains of the epithelial cells. These tubules contained albumin and occasional casts. A few of these tubules were plugged with masses of cellular débris. Other tubules contained a few leukocytes and many red cells. Epithelial cells that were dead were found lining the tubules only occasionally. In several places between the tubules there were rather extraordinary accumulations of large, pale, mononuclear lipoid containing cells resembling exactly the lipoid laden phagocytes seen in xanthoma or occasionally at the site of chronic inflammation where widespread necrosis of tissue has occurred. Most of the glomeruli among the dilated tubules were normal in

appearance but occasionally partly hyalinized glomeruli and adhesions between the tuft and Bowman's capsule were seen. There were infiltrations of mononuclear wandering cells of all sorts beneath the epithelium of the pelvis (figs. 3, 4 and 5).

The liver, lungs, parathyroids, suprarenals and other organs showed no striking pathologic changes.

COMMENT

This disease is very uncommon. Its pathogenesis is little understood. There is no evidence that syphilis or any of the acute illnesses that are known to cause nephritis, such as scarlatina, diphtheria or tonsillitis,

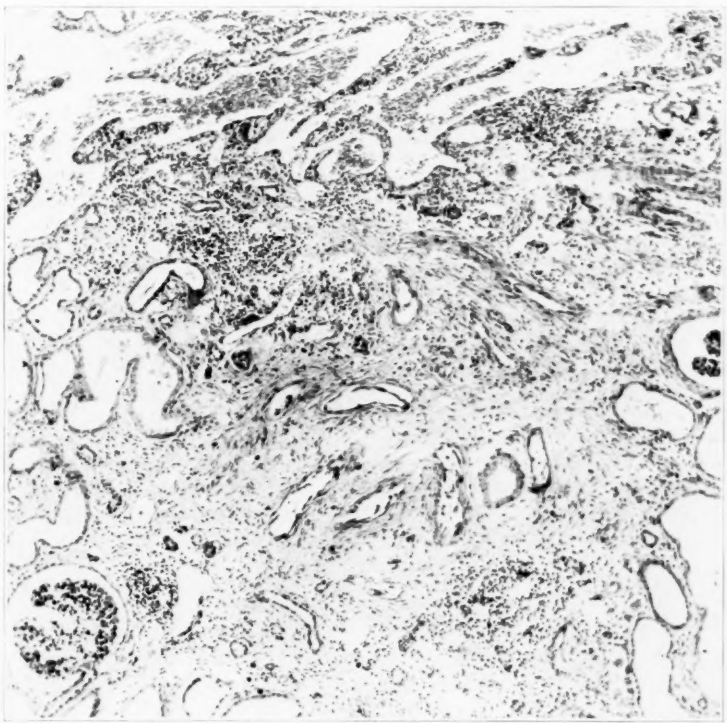

Fig. 5.—Scarring of kidney.

play any rôle in the production of the disease. There is absence of hypertension, cardiac hypertrophy or vascular sclerosis. This would clearly differentiate this type of nephritis from that described by Greene.[9] As more cases come to be reported, however, this distinction may prove to be purely an arbitrary one. In our case the picture is somewhat confused by a chronic infection of the entire genito-urinary

9. Greene, C. H.: Am. J. Dis. Child. **23**:183 (March) 1922.

tract. It would suggest in some respects a chronic cystitis and chronic pyelitis with pyelonephritis and destruction of the kidney parenchyma as secondary effects. It is, however, impossible to say which was primarily responsible for the loss of renal substance. It might be either a chronic interstitial nephritis with secondary infection of the renal tract or an ascending infection of the renal tract with secondary invasion of the kidney.

In most of the cases reported, the lesion is that of chronic interstitial nephritis. In our case there was found an extreme reduction of kidney substance, with some areas resembling chronic nephritis but associated with chronic pyelitis and chronic cystitis. The end-result, however, is identical—an almost total destruction of the kidney parenchyma with very little disease of the blood vessels.

In the patient described here all the characteristic symptoms as given in previously reported cases were present, i. e., the insidious onset in the second decade, the nausea and occasional vomiting, frontal headaches, dwarfish, knock-knee, polydipsia, polyuria and nycturia, with anorexia, air hunger and uremic coma as the terminal events. The physical examination also was similar, showing as it did dwarfism, absence of secondary sexual characteristics, normal blood pressure and normal sized heart, genu valgum, rosary and thickening of the epiphyses, a urine of low specific gravity and albumin with very few casts, a low phthalein excretion, and increased nonprotein nitrogen of the blood.

It is unfortunate that the British authors have been unable to furnish any figures as to the chemical constituents of the blood that we might use for comparison. We were privileged to obtain studies of certain of the chemical constituents of the blood in the case reported here over quite an extended period (table 2). Two and one-half years before death the nonprotein nitrogen was 74 mg. per hundred cubic centimeters, and for more than a year repeated observations showed that it was constantly in the neighborhood of 100 mg. The creatinine also was surprisingly high over a long period. The calcium and phosphorus figures are particularly interesting and show a complete reversal of the normal values. The calcium was in the neighborhood of 5 mg. instead of the normal of about 10, and the phosphorus was over 9 mg., the normal being between 4 and 5. The acidosis with a carbon dioxide capacity of 30 per cent by volume is of note in the absence of any hyperpnea or other untoward symptoms. It is interesting that in a case of such severe renal insufficiency with maximal nitrogen retention over a long period, at no time except in the terminal stage was there any degree of hypertension.

One of the peculiar problems that this case presented was the absence of tetany in spite of a blood calcium of less than 5 mg. At no stage was there the slightest clinical evidence of tetany, though on

frequent occasions attempts were made to elicit Chvostek's and Trousseau's signs. Pincus [10] has shown that cases of chronic nephritis with a low blood calcium are free from convulsions if the free calcium is about normal. In this case, although the total calcium was very low, we found the free calcium to be 3.8 mg., which is entirely normal and above the level at which tetany occurs. It is an interesting speculation that the severe acidosis in this patient may have been a factor in keeping the greater part of the calcium in the circulating blood in the ionized form, and thus may have been a factor in preventing the onset of tetany. Fairly large doses of alkalis (300 cc. of 4 per cent sodium bicarbonate intravenously in one dose, and 1,600 cc. of 5 per cent sodium bicarbonate per rectum over a period of three days—92 Gm. in all) were employed to combat the extreme acidosis of the terminal stage, but this was only sufficient to raise the carbon dioxide capacity from 19 to 24 per cent by volume, still below her previous figures, so that one could not have expected to produce tetany from these therapeutic alkaline procedures.

The pathogenesis of the bone deformity is an even more interesting problem. Clinically the genu valgum, rachitic rosary and thickened epiphyses are difficult to differentiate from the similar deformities found in true rickets. Moreover, at the necropsy table microscopic examination of the costochondral junctions shows in some places an irregularity of the epiphyseal line with islands of osteoid tissue very similar to the picture seen in true rickets. However the roentgenogram shows nothing suggestive of rickets (fig. 2). There is not the irregularity of the epiphyseal line that is seen in that disease, and there is none of the density of an old healing process such as would certainly be present with such a blood calcium and blood phosphorus as this case shows. The picture is merely that of delayed ossification. Moreover, the blood calcium and phosphorus are distinctly outside the rachitic zone, according to Howland and Kramer's figures.[11] They have shown that in the vast majority of cases there is a calcification zone, when the product of the blood calcium and phosphorus is between 30 and 40; that with a product above 40 active rickets is excluded, and with a product below 30 rickets is almost invariably present. The products of 42, 43 and 54 in this case would seem to place these figures well above the rachitic level. The low calcium content of this patient's blood may possibly serve to explain the lack of calcium deposition in the bones, resulting in a softening of the long bones and in abnormalities of the epiphyseal growth. There is evidence to show that the late stages of renal insufficiency are often associated with an increase in the phosphorus content of the blood,[12] which is associated

10. Pincus, J. B.: To be published..
11. Howland, J., and Kramer, B.: Proc. Am. Pediat. Soc. **34**:204, 1922.
12. Marriott, W. M., and Howland, J.: Phosphate Retention, Arch. Int. Med. **18**:708 (Nov.) 1916.

with a decrease in the calcium content. It may be that it is the extraordinary chronicity of the severe renal insufficiency with resulting low blood calcium in a growing person that permits the development of such abnormalities in the ossification of the bones.

In review, the sequence of events in a typical case of renal dwarfism may be pictured somewhat as follows: A severe renal insufficiency, usually a chronic interstitial nephritis, with no previous illness to excite suspicion, appears in a young child early in the second decade, at the onset of puberty before there is adult development of the osseous system. It seems that the renal lesions are of such a nature that they in some way influence mineral metabolism. That there is a disturbance in the normal relationship between the calcium and phosphorus content of the body fluids, which results in a profound alteration and delay in the normal bony development, we do know. Possibly this disturbance is primarily a phosphate retention, which appears to depress the calcium concentration of the blood. Aside from the defective osseous development and its consequences, the case runs the course of a severe chronic nephritis, with maximal nitrogen retention and, curiously, with little effect on the cardiovascular system. During the latter stages a rather severe acidosis appears, attributable in part to the phosphate retention. Death occurs in uremia before the end of the second decade.

SUMMARY

1. In the case of renal dwarfism reported here, the patient presented the picture of a severe renal insufficiency in association with a curious failure of the development of the bones.

2. Phosphate retention with resulting low blood calcium over a long period may be the cause of the delayed ossification of the bones.

3. The severe acidosis may have been the factor in causing the ionization of a sufficiently large proportion of the calcium to prevent the onset of tetany.

ARACHNIDISM

SPIDER POISONING

EMIL BOGEN, M.D.
LOS ANGELES

REPORT OF A TYPICAL CASE

One late summer evening, a young Mexican laborer, while sitting down in an infrequently used outdoor toilet in a suburb of Los Angeles, felt a sharp prick on the end of the glans penis. On looking down he saw a coarse web spun across the hole in the seat of the toilet, and a shiny black spider with a red spot on its belly scurrying to a corner of the web. After the first momentary stinging he felt no further pain in the penis, but about ten minutes later he began to feel a cramping, aching pain in the groins which rapidly spread over the abdomen, legs, back and chest, increasing in intensity for about an hour. He arrived at the Los Angeles General Hospital about six hours after the bite, writhing in agony, and complaining of nausea, vomiting, and of some difficulty in breathing.

The face was flushed, the pupils somewhat dilated, the respiration accelerated, and the knee jerks and other reflexes overactive. The abdominal wall was extremely rigid, suggesting the boardlike rigidity of a perforated gastric ulcer, although there was no marked local abdominal tenderness. A tiny red spot, barely discernible, marked the spot where he had been bitten. The temperature was normal on admission, but rose to 100.6 F. by the next afternoon, while the pulse, which was 100 on admission, fell to 64. The blood pressure was 160 systolic and 90 diastolic, but fell to 130 systolic and 80 diastolic within twenty-four hours. A trace of albumin and a few hyaline casts were found in the urine. The patient had no bowel movements until after he had been given a cathartic on the second day, and he had some difficulty in voiding urine on the first day. The white blood count was 15,000 on admission, with 80 per cent of polymorphonuclear leukocytes, but this dropped to 9,000 by the third day, with 70 per cent of polymorphonuclears. The red blood count was normal, with a color index of 1.

Several hypodermic injections of morphine were given before the patient secured any relief from the pain, and an interrupted restless sleep followed the additional administration of 3 grains (0.1 Gm.) of phenobarbital. The morning after admission he was bathed in a profuse cold sweat, and complained of more pains in the feet and legs, and a numbness that persisted for several days in the soles of the feet. By the second day he was able to sit up, and four days after the onset of symptoms he left the hospital, walking but still weak and afflicted by a little numbness and tingling of the feet.

THE LOS ANGELES GENERAL HOSPITAL SERIES

Fifteen patients have been treated for poisonous spider bites at the Los Angeles General Hospital in recent years. They were all males, ranging in age from 2 to 65 years, but more than half were young adults. Five were Mexican, one negro, two foreign born, and the other seven native whites. Six were common laborers, eight skilled workers, and one was an infant. Five of the bites occurred within the city of Los Angeles, the other ten in the suburbs. Most of them happened in the evening or early morning in the summer or early autumn. Thus, five occurred between 8 and 9, and four between 9 and 12 p. m., and

one occurred at 3 and four between 8 and 11 a. m. There was only one instance each in April, May and October, but two patients were bitten in June, five in July, two in August and three in September. The spider was located in a toilet in eleven instances, in a factory once, and in bed once. Most of the patients had seen the actual spider, which they described as black and shiny, and several mentioned a red spot on its belly.

The bite occurred on the penis in ten patients, the scrotum in two, the back in two, and the abdomen in one. Local signs consisting of one or two tiny pink or red spots were found at the site in eight cases, and local symptoms in that region, after the first momentary prick, were complained of in five. The chief symptom in every instance was pain. This was described by seven patients as severe; by three patients each as continuous or aching; by two patients each as sharp, dull, stinging, cramping, or doubling up, and by others as considerable, great, burning, throbbing, cutting, tingling, shooting, rheumatic or generalized. The pain was located in the legs in eleven cases and in the abdomen in nine, but was also in the chest, back, arms and penis in five cases each, and in the groin in three cases and all over in four.

Perspiration, restlessness and vomiting were complained of by seven patients; constipation by six; nausea by four; difficulty in breathing by three; dizziness, chills, urinary retention, incoordination and edema of the face and of the legs by two, and hiccough, thirst and cough by one patient each. Thirteen patients appeared to be in agony on admission; cyanosis was seen in five; the pupils were dilated in two, were small once and irregular once, and a heart murmur was heard in one. The abdomen was rigid in twelve patients, but tender in only three. The knee jerk and other reflexes were overactive in seven cases; tremors and twitching were found in four, and priapism was noted once.

The pain appeared immediately in six cases and within a quarter of an hour in six others. It reached the maximum severity within a quarter of an hour in three cases; in an hour in five cases; in two hours in three, and in four hours in two. Three patients were seen at the hospital within two hours after the bite; four within six hours; five within twelve hours, and the others within forty-eight hours. The diagnosis was not made definitely at the time of admission in the first five cases admitted, perhaps because we were not then familiar with the condition, for there has been no hesitancy in recognizing the last ten cases, eight of which occurred within the year 1925. The differential diagnosis included infection following insect bite, an acute surgical abdominal condition such as ruptured gastric ulcer or acute appendicitis with peritonitis, renal colic, food poisoning and lobar pneumonia.

Eight patients had a subnormal temperature at the time of admission, but in nearly all a mild fever developed during their hospital stay, in

six instances reaching 100 F. or more, but in no case going above 101.6 F. The pulse was generally retarded as compared with the temperature, being below 72 in half the patients on admission and falling below 66 in the majority during their first few days in the hospital. The respiratory rate was generally slightly accelerated on admission, but soon came down to 20, which was the average rate during the remainder of their stay in the hospital. Two patients had urinary retention requiring catheterization on the day of the bite, and almost all were constipated, going one, and in six cases two, days without a bowel movement.

Fig. 1.—A tarantula, a trap-door spider and three Latrodectus mactans.

Hypertension was found in every patient examined, the blood pressure averaging 150 systolic and over 87 diastolic on admission. Repeated readings, however, showed a rapid drop, the systolic averaging only 136 on the day after admission. Urinalysis showed a trace of albumin in three cases, with hyaline or granular casts in four, pus cells in three and indican and blood in one case each. Stool examination revealed blood in one case. The Wassermann test was four plus in two cases, two plus in one, suspicious once and negative eight times. Leukocytosis was present in almost every case, averaging 14,761 in the nine cases examined on the day of admission, 11,600 in the five cases

examined on the second day, 10,720 in the four cases examined on the third day in the hospital, the highest count being 21,000 on admission, and the lowest 5,900 several days after the bite. There generally was a relative polymorphonuclear leukocytosis, averaging 80 per cent in the eight cases recorded. The red blood cell count was not constant, averaging 5,000,000 in the seven cases recorded, with an average hemoglobin estimation of about 85 per cent. Altogether more than sixty physicians saw these patients while they were in the hospital.

The treatment at the hospital consisted mainly of sedation, with morphine or codeine in ten cases; barbital compounds in seven, hot applications in four; atropine and salicylates in two, and chloral and bromides in one case each; of stimulation, with aromatic spirits of ammonia in three cases; caffeine in two and strychnine once; and of elimination, with magnesium sulphate or citrate in seven cases; castor oil, sodium bicarbonate or enemas in three, and calomel or gastric lavage in one case each.

About six months ago it was felt that, even though we have not yet had a fatality at the Los Angeles General Hospital, it would be advisable to seek some more efficient mode of treatment, since these patients respond so poorly to opiates and require such large doses to give them relief. The use of convalescent serum was suggested, and accordingly 20 cc. of blood, taken from a patient who had recovered from a severe poison spider bite inflicted ten days before, was given intramuscularly to a man who had just entered the hospital in the agony of pain from a spider bite. Since he seemed to be quite improved after the injection, a quantity of blood has been taken from all patients who recover from poisonous spider bites since then, and the serum separated and kept on ice for use in succeeding cases. Only four cases have been so treated up to the present time, but in each of these the relief was felt within a few hours after the injection, and comparative ease was afforded in a much shorter time than would have been expected.

REVIEW OF THE LITERATURE *

Despite the prevalent popular belief in the poisonous nature of spider bites, entomologists and arachnologists [34, 89, 289, 434] have been almost unanimous in asserting that they are harmless, and medical men have been accused of unscientific readiness to accept popular reports of spider bite poisoning without establishing the truth of the facts stated.[105, 358] A spider bite, as any other wound, may easily become infected, and so we find that undoubted cases of tetanus,[251] anthrax,[155] erysipelas,[414] cellulitis [348] and septicemia,[124] confirmed by necropsy and bacteriologic

* On account of lack of space, the bibliography to this article appears in the reprints only.

examinations, have arisen from spider bites. Moreover, the very measures adopted for the treatment of the spider bite may in themselves be the cause of some of the symptoms reported,[55] as the local sloughs following the injection of aqua ammonia,[385] or the symptoms of intoxication following the free imbibition of "stimulants" [112] and the possibility of coincidence must always be borne in mind.[214]

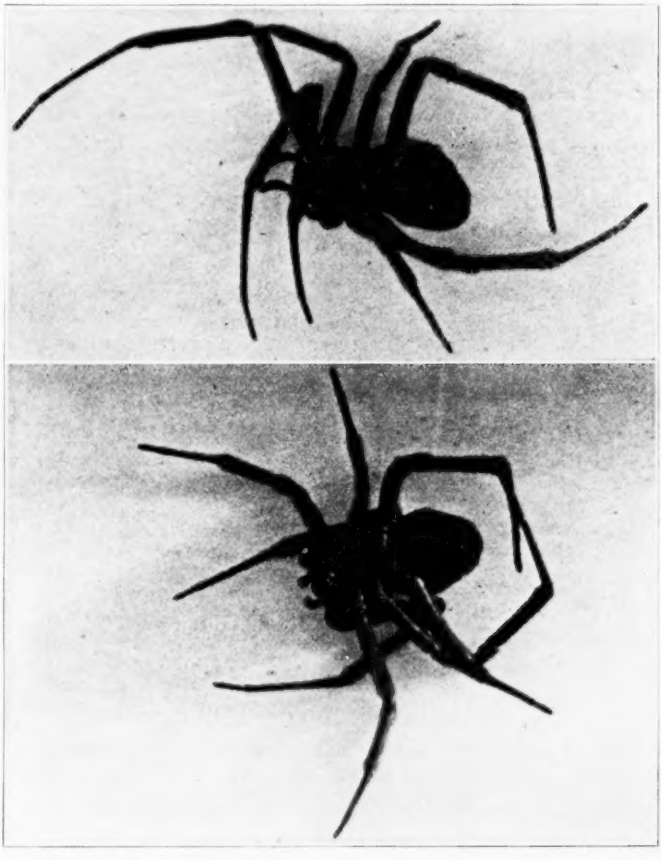

Fig. 2.—Latrodectus mactans.

Nevertheless, the positive evidence of hundreds of careful observers cannot be lightly disregarded. Dangerous illness and even death from the bite of *Latrodectus tredecimguttatus* have been repeatedly described in Spain,[167] France,[93, 106, 177, 247] Italy [75] and Corsica.[76, 341] Dozens of articles have recorded severe results from the bite of related species, *Katipo* in Australia [140, 307, 331] and New Zealand,[151, 360, 445, 458] *Karakurt* in Southeastern Russia,[241, 311, 336, 421] and *Mena vodi* in Mada-

gascar.[64, 146, 429] In South America the poisonous effects of the bite of spiders have been studied both in the clinic and in the laboratory by more than thirty writers. The South Americans describe necrotic, icterohemorrhagic and exanthematous forms of arachnidism caused by the bite of different varieties of spiders in the tropics but all agree that *Latrodectus mactans* causes only a neurotoxic form of the disease with little or no local phenomena.[2, 10, 131, 154, 155, 205, 255, 283, 395, 398]

THE LATRODECTUS MACTANS

Latrodectus mactans is the chief and perhaps the only really poisonous spider in the United States. Besides its many scientific synonyms,[334] including the names *Latrodectus formidabilis, perfidus, dotatus, zorilla, intersector, apicalis, variegatus* and *thoracicus,* and *Theridium verecundum, lineatum* and *carolinum,* it has been given many popular nicknames, such as the "black widow,"[228] the "hourglass" spider,[204] the "shoebutton" spider, the "T bar" spider, the "po-ko-moo"[295] and simply the "poison" spider. Although it is encountered mainly in the southern half of the United States, from the Atlantic to the Pacific coasts, specimens have been reported from such northern states as New Hampshire,[89] New York, Pennsylvania and Ohio.

Latrodectus mactans is a shiny, coal black spider, usually brilliantly marked with red or yellow or both. The female, which is always the one responsible for the bites reported, is often a half-inch in length when fully grown, and may stretch its slim glossy black legs over as much as 2 inches (5 cm.). The markings vary greatly, the most constant being a bright red patch shaped somewhat like an hourglass, on the ventral surface of the abdomen. The globose abdomen, much larger than the cephalothorax, resembles a black shoebutton, although it may have one or more red spots along the middle of the back and over the spinnerets, in addition to the ventral patch. The male is much smaller than the female, and is even more conspicuously marked, having four stripes along each side of the abdomen, in addition to the marks of the female. The young spiders are much lighter in color, gradually donning the glossy black coat in a series of moults over about forty days.[302]

The black widow, as it is called from its custom of eating its mate, is usually found alone, as it will engage in mortal combat with any other spider placed near it. It builds a coarse and irregular dark web in dimly lighted places where it may be undisturbed. Occasionally it is found under stones or pieces of wood or in holes in the ground, in old stumps or bushes, more often in the rafters and corners of little used buildings, in the basements and attics of unfrequented houses, and in the dark corners of barns and other outbuildings, and it has been frequently seen in outdoor toilets, where it builds its web across the seat of the toilet.

AMERICAN CASES

More than 150 cases of poisonous spider bites have been reported by thirty-three physicians in the United States during the last century. Two thirds of these occurred in California, but the others were scattered over more than a dozen states, including Florida, Virginia, Georgia, North Carolina, Alabama, Texas, Oklahoma, Maryland, Pennsylvania, Tennessee, Ohio, West Virginia and Arkansas. More than 80 per cent of the victims were males, and the majority were bitten on the penis or adjacent parts while sitting in an outdoor toilet; others on the hands, feet or other exposed parts. All ages have been reported. A minister and a college professor have not been spared, but most of the victims were farmers or rural laborers, as might be expected from the habitat of the spider. Most of the bites occurred either in the early morning or in the evening in the summer or autumn, but this was not the invariable rule, as cases have been known in almost every month of the year. The spider actually causing the bite was captured and identified by arachnologists in about a dozen cases, but usually it was described as a shiny black spider, and the red spot on the abdomen was frequently mentioned.

A stinging or sticking sensation was noted at first, but this soon disappeared, and except for a tiny red spot sometimes seen, there was no mark or swelling to indicate the location of the bite. In less than half an hour, however, the characteristic pain appeared, increasing in severity for several hours. It has been vividly described as intense, violent, agonizing, exquisite, excruciating, griping, cramping, shooting, lancinating, aching and numbing, and was either continuous and incessant or paroxysmal and intermittent. It was felt in the abdomen and generally also in the legs, back, chest and "all over," less often in the head, shoulders and arms. The pain spreads from the site of the wound by continuity; thus, the patients bitten on the penis usually have pain in the groin and then in the abdomen, while those bitten on the wrist have pain in the arm and then the chest before it reaches the abdomen, suggesting that the venom spreads by the lymphatics and acts in the muscles rather than in the central nervous system. The final distribution of the pain, disregarding the order of development, however, appears to be fairly uniform, irrespective of the site of the initial lesion, and the pain in the abdomen and legs follows bites of the wrist or back just as regularly as it does those of the penis or ankle.

In addition to the acute pain, which was evidenced in most cases by writhing, rolling, doubling up, muscle spasms and paroxysmal contractions, many other symptoms were described. The most common, in the order of frequency, include profuse cold sweats, restlessness, anxiety, difficulty in breathing, anorexia, nausea and vomiting, constipation, cyanosis, delirium, prostration, shock, insomnia, speech dis-

turbances and acute urinary retention. Tremors, twitching, paralyses, convulsions, localized swelling of the bitten part, or of other tissues, chills, dizziness, priapism, jaundice and a macular skin eruption were also encountered.

An extreme boardlike rigidity of the abdomen was the most striking physical finding, but abdominal tenderness was rarely mentioned. Circulatory disturbances, evidenced by cyanosis and an unduly slow or rapid pulse were often noted, but actual figures were lacking. The patients were usually seen by the physician within a few hours after the bite, but the diagnosis was not always made at once, and in several instances the patient was operated on by mistake for an acute appendicitis [438] or other acute surgical abdominal disease, while biliary or renal colic, acute pancreatitis, ruptured gastric ulcer and various forms of poisoning were suggested in others. The most acute symptoms lasted a number of hours, no relief being felt for more than six hours in half the cases reported. The pain then generally subsided in from twelve to forty-eight hours after the onset, but complete ease was often not secured for more than a week, and many complained of weakness and recurring pains for many weeks thereafter.

Seldom in medicine will one find a greater diversity of therapy than in the recorded cases of spider bite. More than seventy-five different remedies have been administered, each with the greatest apparent confidence that this was the best line of treatment. Morphine, whisky or brandy, aqua ammonia or spirits of ammonia, atropine, magnesium sulphate, hot baths and fomentations, enemas, blood-letting, opium or tincture of opium, strychnine, camphor and potassium permanganate have been most commonly employed. Among the other medications mentioned we find amber, arsenic, antimony, acetylsalicylic acid, aconitine, boneset, calomel, cantharides, cocaine, castor oil, Dover's powders, Darby's fluid, Echinacea, edgeweed, elaterium, glonoin, hyoscine, hoarhound, ipecac, lavender, mustard plasters, milk, magnesium phosphate, mercuric chloride, belladonna, nitroglycerin, olive oil, potassium acetate, iodide and carbonate, phenol, plantain, rue, quinine, sinapisms, spirits of turpentine, squirrel's ear, senna, sodium chloride, tansy, tartar emetic, tobacco poultice, valerian, volatile liniment, and Wizard oil.

There is a widespread impression that *Latrodectus mactans* may cause death, and indeed this is not improbable. The closely allied species, *Karakurt* in Russia, *Malmigniatus* in Spain, and *Scelio* in New Zealand, have all been reported as causing considerable loss of life, and in South America many lethal cases have been reported. About ten deaths have been definitely ascribed to the bite of *Latrodectus mactans* in the United States, but only a few of them, as the cases of Dick in North Carolina,[112] Reese in Oklahoma,[354] and Clark in California,[56] have been described in detail. Here the symptoms appear to have been

the usual ones, perhaps a little more severe, and death ensued in from fourteen to thirty-two hours. Heavy dosage with alcohol may have helped to bring on this fatal termination in certain cases, as has been stated, but this will hardly account for all. One victim had been bitten twice by the spider. However, no patient with spider bite has ever died at the Los Angeles General Hospital, nor can we find any record of a case coming to necropsy in the United States.

EXPERIMENTAL STUDIES

The literature of experimental studies of poisonous spider bites is highly conflicting and confusing. Walckenaer,[434] Blackwall,[33] Duges,[121] Doleschall,[116] Bertkau,[31] McCook [289] and Simon [392] allowed themselves to be bitten by various spiders, and Lucas [267] and Bordas [39] reported bites by *Latrodectus;* all stated that they were unable to detect any sign of systemic poisoning resulting from the bite. On the other hand, the

Fig. 3.—Young male white rat bitten by female Latrodectus mactans: it developed a humped back, an almost paralytic gait and sluggish behavior; two days later it died.

careful experiments of Baerg,[14] who received a spider bite on the finger under well controlled laboratory conditions, and reports most vividly on the severe symptoms that followed, which caused him to remain in the hospital for several days, are not lightly to be disregarded.

Injections of extracts, and transplants of the poison glands of *Latrodectus mactans* into rabbits and guinea-pigs without any effect [271] were reported by George Marx in 1889. A few years later, however, Frost reported causing death in one rat and severe symptoms in another with a bite from *Latrodectus scelia,* but that a dog was practically unaffected.[151] Breeger asserted that the poison of *Latrodectus karakurt* was sufficient to cause death in warm blooded animals in almost infinitesimal doses.[51] In 1902 Rudolph Kobert reported that an extract of this spider was highly hemolytic and decidedly poisonous to dogs.[240] About the same time Sachs,[369] in Ehrlich's laboratory, reported an extensive series of experiments showing that the extract of the garden spider contains a powerful hemolysin. In 1914 Castelli [75] in Italy

stated that an extract of *Latrodectus tredecimguttatus* injected into rabbits and guinea-pigs produced death very quickly. The next year Coleman [87] of California stated that an extract of the poison gland of *Latrodectus mactans* caused convulsions and death in a cat, and that a suspension of the spider's eggs was lethal on injection into a cat and a rabbit. He also asserted that there were curious effects from the oral administration of a dry powder prepared from the gland, and attempted its use in therapy. In 1923 Baerg [14] of Arkansas found that the bite of *Latrodectus mactans* produced a definite chain of symptoms in a young white rat, and that an immunity was developed after repeated bites.

In view of the contradictory results summarized above, it appeared desirable to repeat certain of the experiments and so obtain a first hand knowledge of the effects of spider poison on warm blooded animals. Repeated injections of macerated suspensions of *Latrodectus mactans*, as well as solutions of the expressed poison glands, were made in a number of animals, including rabbits, chickens, cats and white rats, without noticeable effect. There was no evidence of any hemolytic effect either in the tissue extract or the suspension of the poison gland as tested against the blood corpuscles of rabbit, sheep and man. The bite of the spider, however, produced the definite symptoms described by Baerg in a young rat, as may be illustrated by a report of a typical experiment.

Jan. 8, 1926, a female *Latrodectus mactans* was applied to the penis of a young male white rat until it took a firm bite. The rat squealed at the bite, and a few minutes later it arched its back in a sort of a hump and appeared to be very dejected and depressed. The next day motion pictures were taken (fig. 3), demonstrating the almost paralytic gait, humped back and sluggish behavior of the rat. Two days later it was found in the cage, dead and partially eaten by the other rats.

CONCLUSION

There is a peculiar, striking and characteristic chain of symptoms following the bite of *Latrodectus mactans*, a poisonous spider common in North America. An exhaustive examination of the available literature on poisonous spider bites in all corners of the earth and an analysis of 150 cases that have been reported in the United States have been attempted. The experimental studies previously made have been reviewed, and additional experiments performed to elucidate some of the moot points. Constant characteristic symptoms have been produced by the bite on a young white rat. It is concluded that the foregoing warrants the acceptance of arachnidism, or spider bite poisoning, as a true clinical entity in the field of general medicine.

NONTRAUMATIC LEFT DIAPHRAGMATIC HERNIA

CLINICAL AND ROENTGENOLOGIC STUDIES IN FIFTEEN CASES *

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AND

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PHILADELPHIA

In reviewing the literature on diaphragmatic hernia, it may be noted that the condition was discovered only seven times in 25,000 roentgenologic examinations, according to the separate reports of Beclere,[1] MacMillan,[2] and Rendich.[3] The Mayo Clinic records finding twenty cases up to July, 1924, or one in about every 18,000 patients examined. According to Carman,[4] fifteen of these were found in the years 1923 and 1924. Richards [5] has tabulated 137 cases taken from the literature from 1900 to 1923. These were all nontraumatic and of the esophageal variety. It is worthy of note that up until 1923 only forty-seven cases had been diagnosed during life.

While these figures would create the impression that the condition is rare, this is not the case. The more general employment of the roentgen ray with its recent advances in diagnosis makes it apparent that diaphragmatic hernia has frequently been overlooked in the past. Morrison,[6] for instance, detected forty-two diaphragmatic hernias in 3,500 roentgenologic examinations of the gastro-intestinal tract. It is proposed in this article to confine our remarks entirely to the question of nontraumatic hernia, fifteen cases of which, all on the left side, were observed and studied by us. In all, sixteen cases, which include one of traumatic origin, were discovered in approximately 9,000 gastric cases studied.

On the basis of an exhaustive embryologic study of the origin of these hernias, Richards [5] has classified them as follows:

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* From the University of Pennsylvania Hospital.

1. Beclere, quoted by Morrison, L. B.: Diaphragmatic Hernia of Fundus of the Stomach Through Esophageal Hiatus, J. A. M. A. **84**:161 (Jan. 17) 1925.

2. MacMillan, quoted by Morrison (footnote 1).

3. Rendich, quoted by Morrison (footnote 1).

4. Carman, R. D., and Fineman, Solomon: Roentgenologic Diagnosis of Diaphragmatic Hernia with a Report of Seventeen Cases, Radiology **3**:26 (July) 1924.

5. Richards, L. G.: Nontraumatic Hernia of the Diaphragm: An Embryological Viewpoint, Ann. Otol. Rhinol. & Laryngol. **32**:1145 (Dec.) 1923.

6. Morrison, L. B.: Diaphragmatic Hernia of Fundus of the Stomach Through the Esophageal Hiatus, J. A. M. A. **84**:161 (Jan. 17) 1925.

1. True hernias (those with hernial sack).
   (*a*) Congenital (present at birth).
   (*b*) Acquired (through a natural opening, usually the esophagus).
   (*c*) Elsewhere—traumatic or nontraumatic.
2. False hernias (without sack)—90 per cent of cases.
   (*a*) Congenital.
   (*b*) Acquired (all traumatic).
3. Eventration of diaphragm (not true hernia).

Diaphragmatic hernia, as the name implies, is a protrusion of any of the abdominal viscera into the thoracic cavity through a congenital or an acquired opening in the diaphragm. The opening may be a normal one which has become enlarged, it may be an artificial one acquired by injury, or it may be present abnormally as a result of impaired development. Depending on whether the hernia has a sack or not, it is called true (with a sack) or false (without a sack). The sack when present consists of a layer of pleura or peritoneum or both. The true and the false type of hernia may be congenital or acquired. By far the commonest type is the congenital false variety, which comprises 90 per cent of the congenital type of diaphragmatic hernias. The acquired false hernias are all traumatic, and are ordinarily thought to be the most common type, although in the present series of cases in only one could a history of trauma be elicited. They therefore are considered congenital. LeWald believes that all cases in which an abdominal viscus is found in the thoracic cavity should be regarded as congenital unless there is overwhelming evidence that the condition has been acquired. It is generally accepted that false hernias develop as the result of a defect in the diaphragm, which is thought to be due to imperfect closure during fetal life of the pleuroperitoneal membrane. In the cases of the true hernia, the arrest in the development of the diaphragm occurs at a later period when the muscle is still too weak to offer any resistance, but after the pleura and peritoneum have formed. These structures consequently are involved in the resulting protrusion into the thorax, and make up the sack which establishes the true type.

The abnormal development of the diaphragm in the true type of hernia is thought to be due to a pathologic rather than to a purely embryologic disturbance such as occurs in the false hernias. Nontraumatic hernia, particularly of the congenital type, has been thought to occur less frequently than traumatic. In this series of cases, however, all were nontraumatic but one. Partially because of the absence of trauma this type is invariably unsuspected and rarely discovered except accidentally. True hernias of the esophageal variety, according to Tonndorf,[7] are due to a malformation developing at a very early embry-

7. Tonndorf, F.: Hernia of the Diaphragm as a Result of Inhibition of Growth of the Esophagus, Deutsche Ztschr. f. Chir. **179**:259 (May) 1923.

onic period from an inhibition of the growth of the esophagus. He bases this deduction on the anatomic observations in four cases in which dissection was performed. In all four, the esophageal opening formed the hernial ring, and in all the shortened esophagus emptied into the hernia sack. This author suggests that all false hernias, because of the absence of the sack, might more correctly be termed prolapses, or ectopias. Le Wald [8] calls attention to a condition that he terms thoracic stomach. This is a congenital anomaly, and refers to a stomach that develops above the diaphragm and is never found below it. In such cases, it may be shown roentgenologically that the esophagus does not pass through the diaphragm, and no other organs of the abdomen are ever found in the thorax. He emphasizes the importance of differentiating thoracic stomach from eventration. In the latter condition, the stomach is always below the diaphragm, which is considerably elevated.

One might justly get the impression from a review of the literature that any part of the diaphragm is susceptible to herniation, especially any of the natural openings. As a matter of fact, a true hernia through the aortic opening or through the quadrilateral foramen which serves as the opening for the inferior vena cava has never been seen. The great majority of hernias are through openings on the left side of the diaphragm (the ratio to the right side being as 12:1) and they may be either anterior, central, or posterior. According to the report of cases diagnosed, and especially those that come to operation, the esophageal variety is the most common. In this series, twelve of the cases were of the esophageal type, three were central, and one was probably central. Richards believes, however, that the esophageal type is uncommon.

Why the left side of the diaphragm is the usual site for a hernia is not definitely understood. It may be partially explained by the fact that protection is afforded the right side of the diaphragm by the liver below and the right lung above. The free motility of the stomach tends to expose the left side, which is already weakened because it contains the natural openings and because it is formed to accommodate the spleen and the stomach. Furthermore, there are two fibrous bands present on the right side of the diaphragm which reinforce it. In addition to these conditions there are probably embryologic abnormalities present, the nature of which is undetermined. This is especially to be considered in the more frequent left sided hernias, as the formation of this side of the diaphragm is considerably more complicated in the embryo than that of the right side. The theory has been advanced, for instance, that as the left side closes after the right and is consequently more poorly vascularized, but little pressure from the abdominal viscera would be required to interfere with its nourishment and thereby arrest its development.

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8. LeWald, L. T.: Thoracic Stomach: Differentiation from Eventration and Hernia of the Diaphragm, Radiology **3**:91 (Aug.) 1924.

Practically every organ in the abdomen, with the exception of the rectum and urogenital organs, has been known to herniate through the diaphragm. More commonly the stomach, colon or both are found to migrate to the thoracic cavity. In this series of fifteen cases, thirteen involved the stomach alone, one, all of the colon except the descending portion and sigmoid, and one, the stomach and colon.

Displacement of organs normally situated in the thoracic cavity usually occurs as a result of the pressure exerted by the herniated organs. The detection of such displacements should lead one to suspect the presence of diaphragmatic hernia. Because of the frequency of left sided hernias, displacement of the heart toward the right and collapse of the left side of the left lung are the most commonly observed changes in the visceral relations. Secondary herniation through the posterior or anterior mediastinal tissues may ensue, in which case an abdominal viscus herniating through the left side of the diaphragm may be found in the right side of the thoracic cavity.

SYMPTOMS

Symptoms may be entirely absent. If present, as is usually the case, they may be respiratory or gastric in nature. More often they are gastric and suggest disease of the gastro-intestinal tract. As a rule these patients are thought to have peptic ulcer, cholecystitis or carcinoma. If the symptoms are mainly respiratory, cardiovascular disease is usually suspected. Probably the most constant, certainly the most suggestive, symptom present is pain, often of a colicky nature, localized just above the ensiform or in the epigastrium, which comes on gradually and more often when the patient is lying down, especially at night. This point emphasizes a none too well recognized fact, i. e., the importance of eliciting an exhaustive history. The pain may be so severe as to suggest biliary colic, and is apt to radiate through to the back and around to the shoulders. Tenderness is noted in the right upper quadrant, or less frequently in the epigastrium. Regurgitation, especially when in the supine position, frequently occurs, probably as a result of the patent cardio-esophageal opening that is usually found in the esophageal hernias. Morrison [6] found such a patency in all of the series of forty-two cases he reported. It furthermore explains, as he points out, why some patients with these hernias cannot sleep on the back or on the left side without acid regurgitation. At times vomiting, especially in the early morning, is complained of and may give temporary relief. The appetite may be unimpaired and dysphagia is relatively infrequent. Excessive flatulence and belching are commonly present two or three hours after meals. Hematemesis, which further encouraged the diagnosis of ulcer, may occur and may be due to inflammation of that part of the stomach wall

that is involved in the opening. Such cardiorespiratory symptoms as dyspnea and palpitation, which at times may occasion no little anxiety, are less frequently present. They are more apt to be noted in elderly people and especially those with myocardial disease, cardiac hypertrophy and aortitis.

PHYSICAL SIGNS

Physical signs may be absent, particularly in the esophageal opening hernias. Frequently asymmetry of the chest with protrusion of the affected side and displacement of the heart or lungs may be observed. A horizontal area of dulness, which is not absolute, or tympany at the lower boundary of the lung may be found on percussing the patient in the erect position. The area of dulness may move downward with inspiration. The respiratory sounds may be preserved over a hernia, and metallic phenomena as described by Elias and Hitzenberger [9] are to be found in certain cases. Vocal fremitus is usually diminished over the affected area.

DIAGNOSIS

The diagnosis has seldom been made clinically. It can readily be made by the roentgenologist, however, and if made early the patient will often be spared an unnecessary operation for some other suspected cause of his illness. Misleading symptoms which direct suspicion and treatment toward innocent organs invite delay, and the danger of strangulation, even if not great, is always present and greatly adds to the mortality of operation. In making a roentgen-ray diagnosis, the examination should be made after a barium meal, first with the patient in the erect position, thus obtaining anteroposterior and oblique views, and then observations should always be made in the horizontal position. It appears that these hernias are frequently overlooked because the fundus is not filled and the patient's position changed. Repeated attempts to fill the herniated portion of the stomach may be necessary, and more than one examination required. Subsequent examinations of the colon should be made to determine whether or not it is included in the hernia. The roentgenologist can help determine the type of treatment by observing the size and location of the hernia and by noting the symptoms when the hernial sack is filled, and the amount of dilatation of the esophagus. The examination should suggest the site for operation, whether above or below the diaphragm, by determining the position of the diaphragm, the width of the angle at the ensiform, and the extent of ossification seen in the costochondral cartilage. In making roentgen-ray examinations the length of the esophagus may sometimes be determined, but esophagoscopy

9. Elias, H., and Hitzenberger, K.: Comparative Examinations of Patients by Clinical and Roentgenologic Methods: Diagnosis of Hernia and Relaxation of the Diaphragm, Wien. Arch. f. inn. Med. **6**:437 (July 1) 1923.

is the only exact way of determining this in many cases. Patients with a congenitally short esophagus of course are not amenable to surgery. Much of interest from a roentgenologic standpoint, particularly the diagnosis, has been contributed by Carman and Fineman,[4] Reich,[10] LeWald,[5] Ford[11] and Healy.[12]

ROENTGENOLOGIC REPORT OF CASES

In reporting the roentgen-ray findings in the case of esophageal opening hernia of the stomach under discussion, it has seemed worth while to include with this report a record of all the cases of diaphragmatic hernia which have been diagnosed by one of us, and which, so far as we have been able to learn, have never been formally reported. The records of the Department of Roentgenology of the University Hospital show that sixteen cases of left sided diaphragmatic hernia were observed during the last thirteen years, since comprehensive routine fluoroscopic studies have been carried out on gastro-intestinal patients in all necessary postures. This does not include any cases of right sided diaphragmatic hernia. Nearly all the hernias, as is usually the case, were discovered accidentally during routine gastro-intestinal studies. Three hernias through the central portion of the diaphragm were suspected because of findings in chest examinations, and were subsequently studied by opaque meals. One other patient was known to have a hernia and consented to a gastro-intestinal observation to satisfy our curiosity. One central case was traumatic and the other fifteen were congenital. Of all the cases, five were hernias through the central portion and eleven were through the esophageal opening. The latter groups can apparently be divided into two varieties, those in which the esophagus opens below the herniated portion and those in which it opens into the herniated portion of the stomach, the latter seeming to favor larger hernias.

In all the older cases, our roentgenographic records were glass plates, which have been broken or have since disappeared. Fortunately, lantern slides were made in most instances, and serve to show the condition.

CASE 1.—Mrs. W. A. B., aged 61, was examined Dec. 21, 1925. This case is mentioned first for the reason that it was the one that suggested this presentation of the subject. The roentgen-ray examination was made by the double meal method. There was no six hour residue. In the erect posture the stomach was normal in position, size and shape, with the greater curvature at the umbilical level. No peristalsis or motility was observed until the stomach was palpated vigorously, and both then started at a normal intensity and rate. No defects in outline were noted except that in the prone, recumbent and right lateral recumbent postures there was observed an esophageal opening hernia of the stomach

10. Reich, Leo: Roentgen Diagnosis of Diaphragmatic Hernia and Related Clinical Pictures of the Diaphragm, Wien. Arch. f. inn. Med. **6**:445 (July 1) 1923.

11. Ford, Charles: Diaphragmatic Hernia, Radiology **5**:158 (Aug.) 1925.

12. Healy, T. R.: Symptoms Observed in Fifty-Three Cases of Nontraumatic Diaphragmatic Hernia, Am. J. Roentgenol. **13**:266 (March) 1925.

about the size of an egg, above the left diaphragm (figs. 1 and 2). The location of the esophageal entrance into the stomach could not be determined in relation to the herniated portion as there was no regurgitation of food into the esophagus and the hernia could not be seen in the erect posture. There was no esophageal obstruction to either liquids or capsule. The colon in this case was not included in the hernia.

Case 2.—J. B., aged 28, was examined Jan. 13, 1915. This was a traumatic case through the more central portion of the left diaphragm. In the recumbent posture about half the stomach was above the left diaphragm level. Details are omitted as our report was not intended to include traumatic cases.

Case 3.—Mrs. W. S. H., aged 44, was examined March 13, 1915. This patient was referred for a chest examination. She knew she had a left diaphragmatic hernia from previous examinations, and permitted us to examine her stomach as

Fig. 1 (case 1).—Appearance in erect posture, directly after opaque meal.

a matter of interest. By fluoroscope there was revealed in the erect posture a hernia of the upper portion of the stomach through the left diaphragm. The herniated portion seemed to fill directly from the esophagus. After the swallowing of the meal was completed, the pouch above the diaphragm emptied rather rapidly but filled again in the recumbent and prone postures, only to empty again on the patient's resuming the erect posture. We were never able to satisfy ourselves entirely as to whether this was a small central or a large esophageal opening hernia, although appearances favored the former.

Case 4.—Mrs. H. C. I., aged 66, was examined April 14, 1915. She had had indefinite gastric symptoms for several years and ulcer or carcinoma had been suspected. The opaque meal seemed at first to enter the stomach a considerable distance below the fundus, but a little later, there was observed a left diaphragmatic hernia of the stomach. The herniated portion in the erect posture contained

only gas, but quickly filled with the opaque meal when the patient lay on her back or right side and emptied when she lay prone. No other abnormality was found. The colon was not included in this central hernia.

CASE 5.—J. M., aged 13, was examined July 19, 1917. This patient was referred for a chest examination because of chest symptoms and signs. Further than this we are not able to obtain any clinical data. The fluoroscopic record reveals that gas was detected above the left diaphragm, and the patient was then given an opaque meal in the erect posture. It entered the stomach below the diaphragm. A lantern slide shows a small part of the meal and a large collection of gas above the diaphragm in the erect posture. When the patient was placed prone, apparently all the opaque meal was above the diaphragm, and the herniated stomach occupied the lower half of the left chest. Part of the colon was also found above the diaphragm. This was a central hernia.

Fig. 2 (case 1).—Appearance in recumbent posture, showing esophageal opening hernia.

CASE 6.—Mrs. A. A. M., aged 65, was examined Sept. 19, 1918. The stomach was normal in position, size and shape, except that in the prone posture there was noted a small esophageal opening hernia, not evident in the erect posture. The stomach was otherwise negative and there was no esophageal obstruction. The location of the esophageal entrance into the stomach was not recorded.

CASE 7.—C. O. B., a man, aged 55, was examined Dec. 11, 1919. He had a history of indefinite gastric symptoms. The stomach was normal in position, size and shape, and otherwise negative except that in the prone posture an esophageal opening hernia about the size of an egg was noted above the left diaphragm. From this, contents seemed to regurgitate directly into the esophagus quite frequently. There was no esophageal obstruction.

Case 8.—Mrs. R. E. R., aged 68, was examined April 2, 1923. She had indefinite gastric symptoms. The stomach was normal in position, size and shape and otherwise negative except that in the prone posture there was noted a moderate sized esophageal opening hernia above the left diaphragm level. There was no esophageal obstruction.

Case 9.—Mrs. F. W. F., aged 60, was examined Feb. 6, 1924. Vague gastric symptoms were complained of. The stomach was normal in position, size and shape in the erect posture. In the prone and recumbent postures, the fluoroscopic appearance suggested an hour glass constriction just below the fundus, and opposite to it, on the lesser curvature, a Haudek niche. The stomach was otherwise negative and there was nothing abnormal in connection with the swallowing

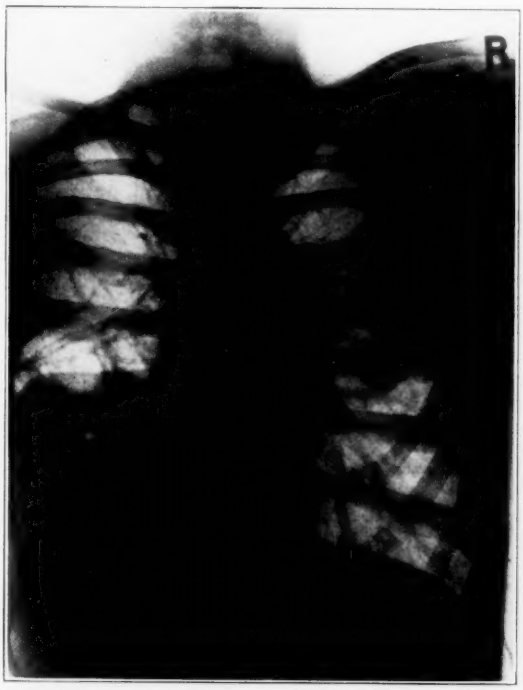

Fig. 3 (case 12).—Chest that presented an appearance suggesting a possible left sided diaphragmatic hernia.

function. The films showed that what was taken for an hour glass constriction was the narrowing at the neck of a rather large esophageal opening hernia above the left diaphragm. The supposed Haudek niche was the entrance of the esophagus just below the constriction.

Case 10.—J. E., a man, aged 54, was examined Nov. 27, 1924. His symptoms were mostly intestinal. With the swallowing of the opaque meal, there was apparently an obstruction of a spasmodic nature in the lower end of the esophagus. This was explained later, however, by the ease of regurgitation of food into the esophagus. The stomach was normal in position, size and shape and otherwise negative except that in the lying positions there appeared an esophageal opening

hernia through a rather large opening, as the gastric constriction was slight. Our interpretation was a comparatively small hernia of the stomach into which a dilated esophagus entered, and in the absence of any diaphragmatic pinch cock, regurgitation occurred very readily on lying down. An esophagoscopic examination by Dr. Chevalier Jackson showed that gastric mucosa began about 6 inches (15.2 cm.) below the left bronchus crossing. The herniated portion of the stomach was more extensive, therefore, than we thought. We could not tell where the esophagus stopped and the stomach began, or how much we interpreted as dilated esophagus was really stomach.

Case 11.—C. R. S., a woman, aged 50, was examined Jan. 8, 1925. She was suffering from indefinite gastric symptoms. The stomach was normal in position,

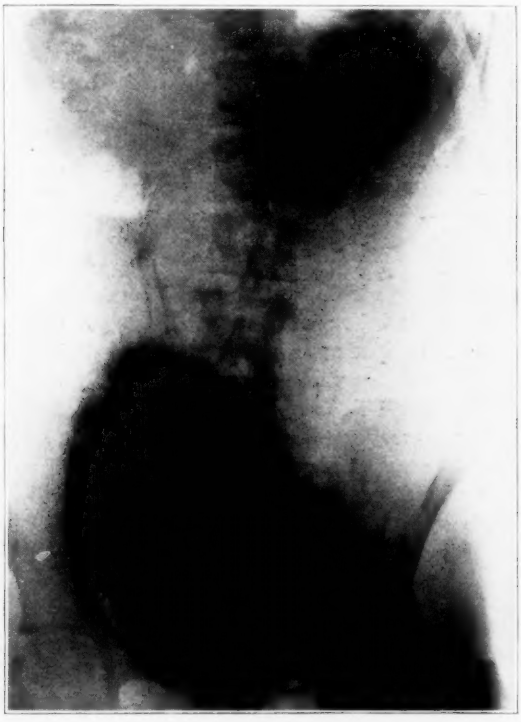

Fig. 4 (case 12).—Extreme ptosis of the stomach.

size and shape, with the greater curvature slightly above the umbilicus. No defects were seen in the stomach or duodenal cap, except that in the recumbent posture a small esophageal opening hernia was observed. The esophagus opened into this portion.

Case 12.—R. C., a man, aged 27, was examined Jan. 8, 1925. His chief complaint was epigastric pain of several years' duration and recent pain in the right lower chest. An examination of the chest showed at the left base an appearance that suggested a possible diaphragmatic hernia (fig. 3). A gastrointestinal examination was then carried out. The examination of the stomach

showed practically a complete six hour residue and we were surprised to find no hernia of this structure in any posture but, instead, a long, low, vertical stomach with the greater curvature on a level with the symphysis pubes. There was a marked intermittent hyperperistalsis with antiperistalsis and no motility, except that in the right lateral recumbent posture it was fairly free. This indicated no pyloric stenosis but suggested that the obstruction was probably mechanical, due to kinking (fig. 4). On the following day, most of the opaque contents in the colon were found in the thoracic cavity. A subsequent barium enema showed all the colon except the descending portion and sigmoid to be herniated through the left diaphragm (fig. 5). After evacuation, the entire large bowel was empty of opaque contents. This case is unusual in the fact that the colon was herniated and the stomach was extremely ptosed. The ileum was never located.

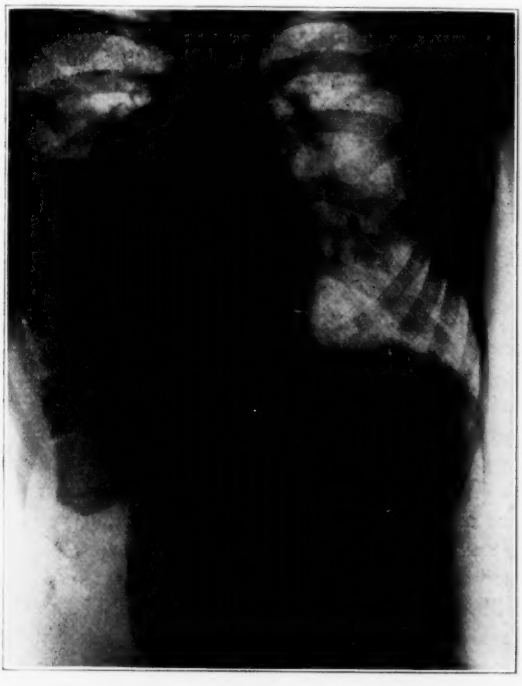

Fig. 5 (case 12).—Appearance after barium enema, showing most of the colon herniated into the thoracic cavity through the left side of the diaphragm.

CASE 13.—Mrs. L. C., aged 49, was examined March 24, 1925. This was a case of carcinomaphobia. The stomach examination was negative except for a small esophageal opening hernia, observed in only the prone and recumbent postures. The point of entrance of the esophagus in relation to the herniated portion of the stomach was not established.

CASE 14.—I. M., a woman, aged 42, was examined Feb. 15, 1926. This was at first regarded as a case of esophageal opening hernia, but a careful examination showed that what was taken for a herniated portion of the stomach was a large diverticulum coming off from the anterior and right aspect of the esophagus just above the left diaphragm. The diaphragmatic opening was large, without pinch-

cock effect, and it was impossible to tell just where the esophagus ended and the stomach began.

CASE 15.—Mrs. B., aged 51, was examined April 7, 1926. The patient had been complaining of gastric distress and gaseous distention with eructations. The examination of the stomach showed slight ptosis, but was otherwise negative, except that in the prone and recumbent postures, there was a small cosphageal opening hernia. The swallowing function was normal.

CASE 16.—Mrs. C. F. H., aged 29, was examined March 18, 1926. She had complained for several years of epigastric distention after eating. Epigastric pain appeared for three or four weeks at a time. The pain was irregular in relation to meals. There was considerable belching but no nausea or vomiting. She felt more comfortable when lying down. The pain frequently came on while the patient was eating, and was accompanied with vertigo. The physical examination revealed nothing of significance. Roentgenologic examination showed a cascade stomach causing almost an hour glass constriction. There was a tendency for gas to collect in the fundus because of the high left diaphragm. When the patient lay in the recumbent postures, the contents seemed to regurgitate into the esophagus. The film indicated a moderate sized esophageal opening hernia. There were multiple points of stasis in the small intestine suggesting slight obstruction. Examination of the colon by barium enema revealed a redundant sigmoid loop, and a very high splenic flexure and transverse colon, which was probably responsible for the cascade stomach. There was a spastic descending colon and upper sigmoid and a large capacious lower sigmoid and rectum.

TREATMENT

There is only one line of treatment for diaphragmatic hernia and that is surgical. Contrary to a widely prevalent belief, operation for this condition is not fraught with the risks commonly attributed to it. The contraindications to operation are greatly overrated, according to Hedblom.[13] This author made a study of 378 patients that came to operation, and believes that while contraindications to surgery do exist, they are not great in comparison with the incapacitation the hernia produces or with the menace to life which its presence involves. It has been estimated that in 15 per cent of cases strangulation occurs and as a result the operative mortality is doubled. In a review of 126 cases in which obstruction ensued, the operative mortality was estimated at 53.1 per cent; in 252 cases without obstruction, it was 23.8 per cent. The mortality in most instances was due to delayed operation in the presence of obstruction, to shock, and to respiratory failure. In considering the approach for operation, it appears, if obstruction is excluded, that the mortality is greater following laparotomy than thoracotomy. It seems, however, that most surgeons prefer laparotomy despite the fact that the dangers from thoracotomy have been reduced to a minimum. Deaver and Ashhurst [14] strongly urge thoracotomy. They believe the prospects of recovery are better as the result of thoracic approach, as the lung is

13. Hedblom, C. A.: Diaphragmatic Hernia: A Study of 378 Cases in Which Operation Was Performed, J. A. M. A. **86**:947 (Sept. 26) 1925.

14. Deaver, J. B., and Ashhurst, A. P. C.: Surgery of the Upper Abdomen, Ed. 2, Philadelphia, P. Blakiston's Son & Co., p. 242.

already collapsed and the heart displaced. Of still more importance, however, is the fact that the existence of negative pressure in the unopened pleural cavity produces suction on the herniated organs, which makes reduction by traction below difficult and dangerous. They believe that laparotomy should be performed only when injury to some abdominal organs may have occurred, in which case an abdominal approach is required to effect their repair. Weichert [15] and others prefer a combined thoracic and abdominal approach. The choice of operation must depend, however, on the nature of the case.

Disregarding the indications that compel operative intervention, such as strangulation and obstruction, it would seem reasonable *not* to operate in cases that are of congenital origin or in those of presumably long standing, especially if they are nontraumatic. In known traumatic cases, early reduction unquestionably is to be advised. In estimating the prognosis in cases in which no operation is done, it is interesting to note that ulceration of a herniated stomach may occur. Kienbock [16] reported thirty-two such cases. In a few instances the ulcer has been known to perforate, thereby causing pyothorax. Peritonitis does not develop under these circumstances, since the abdominal cavity is protected by the muscular ring about the diaphragmatic opening.

In the final analysis, one must appreciate that the presence of abdominal viscera in the thoracic cavity not only is compatible with life, but, what is more amazing, may occasion none or but passing symptoms, and usually is discovered only accidentally at operation for some other condition or at necropsy.

SUMMARY

Diaphragmatic hernia is not as rare as is commonly thought. The more general employment of the roentgen ray with its recent advances in diagnosis make it apparent that the condition has been frequently overlooked.

Sixteen cases were discovered by one of us in approximately 9,000 gastric cases studied. Fifteen were nontraumatic and on the left side. Twelve were through the esophageal opening. Three were central, and one was probably central.

The diagnosis can be made with certainty only by means of the roentgen-ray studies. In the roentgenographic examination of gastrointestinal cases the studies should be made after a barium meal, first with the patient in the erect position, thus obtaining anteroposterior and oblique views, and then observations should always be made in the horizontal position. More than one examination may be required. Sub-

15. Weichert, Max: Operation for Diaphragmatic Hernia, Beitr. z. klin. Chir. **131**:180, 1924.

16. Kienbock: Fortschr. a. d. Geb. d. Röntgenstrahlen, 1914, p. 322.

sequent studies of the colon should be made in order to determine whether or not it is included in the hernia.

The symptoms may be respiratory but are usually gastro-intestinal. The most common and suggestive symptom is pain above the ensiform or in the epigastrium, which comes on particularly in the recumbent position and at night time. Regurgitation when in the supine position usually accompanies the pain.

The recognition of the presence of diaphragmatic hernia is of great value in saving many patients an unnecessary operation for cholecystitis, peptic ulcer, and other common lesions which are often thought to be the cause of their symptoms.

Surgery offers the only line of treatment.

THE REGULATION OF THE FLOW OF BILE AND PANCREATIC JUICE INTO THE DUODENUM *

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Early in our study of the physiology of the biliary tract we were impressed with the considerable influence that the mechanism at the distal end of the common bile duct exerts, not only over the discharge of bile from the common duct into the duodenum but also over the gallbladder. In a previous article it was shown by one of us [1] that the control over the distal end of the common duct is one of the necessary factors for the collection of bile by the gallbladder. This article, one of a series of papers on the liver and biliary tract which have appeared from this department of surgery during the last five years, will report observations concerning some factors involved in the regulation of the flow of bile into the duodenum. A method of the regulation of the flow of pancreatic juice into the duodenum will also be described.

The presence of a control over the flow of bile is evident from the fact that bile may pass intermittently from the common duct into the intestine. This control has been considered by most investigators to be exerted almost wholly by the so-called sphincter of Oddi. A distinct sphincter cannot always be found apart from the fibers of the muscle coat of the intestine. However, it is the opinion of most investigators that such a distinct group of muscle fibers, which could act as a sphincter, is present in most animals and in man. A great many determinations have been made of the pressure in the common duct that the sphincter will withstand. Accurate determination of the pressure, which may be attributed to a common duct sphincter alone, is difficult to obtain because of a considerable number of sources of error.

Our attention was called to the fact that normal tonus of the duodenal wall might be an important factor in the resistance to the flow of bile into the duodenum by observing discharges of bile from the duodenal papilla coincidently with the passage of peristaltic movements along the duodenum of a dog dying of anoxemia. Irritation of the cyanotic intestine caused vigorous peristaltic movements to form in the duodenum which were accompanied by an ejection of bile. Subsequent

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1. Copher, G. H.: Cholecystography: Appearance and Disappearance of the Shadow, J. A. M. A. **84**:1563 (May 23) 1925.

confirmatory experiments were made by opening the duodenum of anesthetized dogs and visualizing the discharge of bile from the papilla with the passage of peristaltic movements initiated by various stimuli. The animal should be fasting previous to this experiment.

During the period of further investigation of this phenomenon, Burget [2] reported his experiments in which he measured the pressure in the common bile duct and observed the tonicity of the intestines. He is of the opinion that undue significance is attributed to the sphincter of the common bile duct. He concludes also that resistance to pressure in the common duct is offered by the normal tonus of the duodenum and that peristalsis of the duodenum is an important factor in emptying the duct by a milking action and by aspiration due to reduced pressure following a peristaltic wave. Pilocarpine and physostigmine were found, through their effect on the tonus of the intestine, to increase greatly the amount of pressure withstood in the duct, while epinephrine and atropine reduced it to a minimum. Burget recognized the significance of the fact that the duct passes obliquely through the intestinal wall.

The common bile duct of the dog runs for a distance of from 2 to 4 cm. obliquely through the wall of the intestine before it enters the lumen. The common bile duct in the human being together with the pancreatic duct perforates the muscular wall of the duodenum and runs obliquely for 1 or 2 cm. between the coats to form an elevation beneath the mucous membrane. In most instances it opens by a common orifice with the pancreatic duct near the junction of the second and third portion of the duodenum.[3] This anatomic arrangement will be shown to constitute a sphincter-like mechanism which is dependent on the tonicity of the intestine and makes it possible for peristalsis to be a factor in emptying the duct.

Carlson [4] is also of the opinion that "the resistance to the flow of bile into the duodenum is probably determined more by the tonus of the muscle wall of the duodenum than by the tonus of the so-called sphincter of Oddi." He does not give experimental data but describes the anatomic relationship of the duct and intestine.

We have performed experiments in which a cannula was placed in the common bile duct of dogs at a considerable distance proximal to the point where the duct entered the intestine. Lateral hepatic ducts, which in the dog join the common duct below the cystic duct, were ligated. Pressure was maintained in the common bile duct by a column of

2. Burget, G. E.: The Regulation of the Flow of Bile, Am. J. Physiol. **74**: 585 (Nov.) 1925.

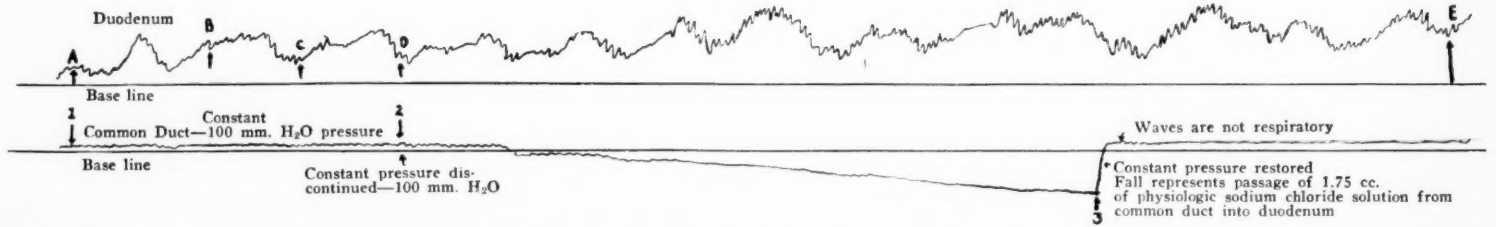
3. Quain's Anatomy, ed. 10, New York, Longmans, Green & Co., part IV, **3**:128; 141.

4. Carlson, A. J.: Physiology of the Liver: Present Status of Our Knowledge, J. A. M. A. **85**:1468 (Nov. 7) 1925.

fluid in a buret which was connected to the cannula in the duct. A pressure of from 50 to 250 mm. of a physiologic sodium chloride solution which varied with each dog was maintained. Variations of pressure and volume in the duct were observed in the buret. They were also recorded by a tambour on a smoked drum. The duodenum was ligated both near the pylorus and approximately 6 cm. below the duodenal papilla. The pancreatic ducts were ligated. Tonus, movements and changes of volume in the portion of duodenum between ligatures were recorded on the drum by means of a glass tube containing physiologic sodium chloride solution, which was held in the intestine by a purse string suture. The results were the same whether we used physiologic sodium chloride solution, bile or a gum arabic solution of approximately the same viscosity as bile. These experiments differ from those of Burget in that not only the pressure in the common duct is measured but also the amount of discharge from the duct. Likewise, changes of tonus and volume in the duodenum were recorded simultaneously with those of the common duct.

A fall of the pressure in the common duct was found to accompany relaxation of tonus of that portion of the duodenum containing intramural duct. Relaxation of the tonus may occur independently of peristalsis. The discharge of the content of the common bile duct into the duodenum may take place during the relaxation phase of a peristaltic movement. This relaxation occurs either with spontaneous peristalsis or induced peristalsis originating from chemical, thermal, mechanical or electrical stimuli. Coincidently, with the fall of pressure in the common duct and the passage into the duodenum of physiologic sodium chloride solution there was usually recorded an increase in volume of the duodenal content (accompanying figure). This increase in volume would not be recorded when there was a general relaxation of the duodenal musculature, although there was an actual increase of fluid in the lumen. Such a relaxation may occur when the loop of duodenum has become fatigued and after the administration of certain drugs. If the pressure in the common duct dropped below a varying minimal figure, there was not a discharge from the duct nor was there an increase of duodenal volume, even with vigorous peristalsis.

We have also, for the first time, recorded an alternate rise and fall of pressure in the common duct simultaneously with rhythmic or pendular movements of the duodenum (figure). These changes of pressure in the common duct, apparently due to rhythmic movements, are independent of the fall of pressure in the duct due to relaxation of tonus. The effect of the rhythmic movements on the common duct results in a second method of regulating the flow of bile. As these movements constrict the intramural portion of the duct, they may aid by acting as a pumping mechanism in the expulsion of bile from the duodenal



The upper tracing records tonus, movements and volume changes in the segment of duodenum between ligatures; *A*, distance of tracing above base line, representing the volume of fluid in the segment at the beginning of experiment; *B*, small wave, corresponding to a rhythmic contraction; *C* to *D*, large wave, representing a peristaltic movement; *E*, volume of fluid in segment of duodenum at end of experiment. Increase of volume over *A* should be noted. The lower tracing records pressure and volume changes in the common bile duct; *1*, small wave, representing change of pressure in duct corresponding to *B*, a rhythmic contraction; *2*, at this point a pressure of 100 mm. of physiologic sodium chloride solution in the duct was started. The fall in pressure is steplike, corresponding to a relaxation phase of a peristaltic movement. *3*, a constant pressure of 100 mm. of physiologic sodium chloride solution was resumed. The fall in pressure from 2 to 3 represents the passage of 1.75 cc. of physiologic sodium chloride solution from the common duct into the duodenum.

papilla. The higher the pressure in the common duct, the more effective will be the emptying of the duct owing to relaxation of tonus of the duodenum and to rhythmic movements. If the pressure in the duct is sufficiently high, it may overcome the tonicity of the duodenal wall so that the bile will enter the lumen without the aid of peristalsis or rhythmic movements.

The evidence that the normal tonus of the duodenum is an important factor in the regulation of the flow of bile is substantiated by the use of drugs. Varying quantities of 25 per cent and 50 per cent solutions of magnesium sulphate were introduced into the duodenal segment. There was never a marked response to magnesium sulphate. Peristaltic movements were not greatly increased and relaxation of the musculature was not great. The fall of pressure in the common duct was correspondingly small.

The injection of 1 or 2 cc. of oleic acid into the duodenal segment caused a great increase of duodenal movements and fall of common duct pressure. The relaxation of tonus of the duodenum was greatest approximately five minutes after introduction of the fatty acid. Oleic acid produced a greater fall of pressure in the common duct than magnesium sulphate. This effect of fats on the duodenum is probably one of the factors in the rapid emptying of the gallbladder after the ingestion of a meal of lipoids and fats as observed by Boyden [5] and by Sosman, Whitaker and Edson.[6] The increased peristaltic activity and relaxation of tonus allow a part of the contents of the gallbladder to pass into the duodenum in the course of two hours.

Intravenous injection of moderate doses of atropine sulphate permits a considerable reduction of pressure in the common duct. It produces a decrease of tonus without greatly affecting the rate or amplitude of peristaltic movements. It is possible, then, for the maximum discharge to take place from the duct during the relaxation phase of peristalsis.

Epinephrine chloride also causes a relaxation of the intestine and a fall in the common duct pressure. The fall is most marked during the rise of blood pressure from epinephrine.

Intravenous injection of pituitary extract is followed by an initial immediate relaxation of the duodenum and a great fall in its common duct pressure corresponding to the rise of blood pressure. The pituitary

5. Boyden, E. A.: The Effect of Natural Food on the Distention of the Gallbladder, with a Note on the Change in Pattern of the Mucosa as It Passes from Distention to Collapse, Anat. Rec. **30**:333 (Aug.) 1925.

6. Sosman, M. C.; Whitaker, L. R., and Edson, P. J.: Clinical and Experimental Cholecystography, Am. J. Roengenol. **14**:495 (Dec.) 1925.

extract, however, quickly increases the tonus and activity of the intestine. There may be a fall of pressure with each relaxation phase, such as occurs normally with peristalsis.

Pilocarpine and physostigmine increase the tonus of the intestine and thereby increase the amount of pressure that the duct will withstand. The increase of tonus is usually so great that in spite of increased movements of the duodenum there is no discharge from the common duct.

It is evident that drugs that affect the tonus of the duodenal musculature affect the discharge of bile from the common duct. There may be a discharge of fluid from the duodenal papilla with each relaxation phase of peristaltic movements in spite of an increase of tonus. The tonus may be so greatly increased, however, that there will not be a discharge from the duct during the relaxation phases of violent intestinal movements.

It was thought likely that tonus of the duodenum exerted the same regulatory control of the flow of pancreatic juice into the duodenum as the flow of bile. A similar method to that used in the preceding experiments was used in recording pressures in the pancreatic duct and changes in the duodenum. A large pancreatic duct in the dog opens into the duodenum a few centimeters below the duodenal papilla. It is comparatively short. The duct passes obliquely through the intestinal wall for a distance of from 0.5 to 1 cm.

There is considerable variation in the relationship of the pancreatic duct and the common bile duct in the human being. The relation in which both ducts enter the duodenum is variable. These variations have been studied by Mann.[7] However, these variations do not alter the general anatomic arrangement of this region given by most textbooks of anatomy. The pancreatic duct of Wirsung in the human being, usually near its termination, comes in contact with the common bile duct, together with which it passes obliquely through the muscular coats of the intestine for a distance of about 1 to 2 cm. and terminates in the ampulla of Vater, situated near the junction of the second and third portions of the duodenum.[4] Hendrickson[8] has shown the intimate relationship of the common bile duct, the duct of Wirsung and their investing muscular coats.

Tonus of the duodenum was found to exert the same regulatory control over the pancreatic duct as over the common bile duct. A fall of pressure in the pancreatic duct accompanies a relaxation of tonus. The same effect is obtained from drugs on the pressure in the pancreatic

7. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, Arch. Surg. **6**:1 (Jan.) 1923.

8. Hendrickson, W. F.: A Study of the Musculature of the Entire Extrahepatic Biliary System, Including That of the Duodenal Portion of the Common Bile Duct and of the Sphincter, Bull. Johns Hopkins Hosp. **9**:221, 1899.

duct as on the pressure in the bile duct. We do not have a record of changes of pressure in the pancreatic duct corresponding to rhythmic movements of the duodenum similar to those found in the common duct.

This regulation of the flow of bile and pancreatic juice that has been described offers an accurately timed mechanism for the efficient admixture of gastric chyme, bile and pancreatic juice. A relaxation period between peristaltic movements, during which time bile and pancreatic juice enter the duodenum, allows the chyme and secretions to be mixed together by rhythmic contractions. A peristaltic movement following a relaxation period sweeps this bolus of chyme and secretions down the intestine. The process is then ready to be repeated.

CONCLUSIONS

Tonus and peristalsis in the duodenum are of great importance in the regulation of the flow of bile into the duodenum. This control is independent of factors other than pressure of the bile in the common duct. The duodenal wall exerts a like control over the discharge of pancreatic juice from the pancreatic duct. Food, drugs and chemicals that affect tonus and peristalsis are factors in the regulation of the flow of bile and pancreatic juice into the duodenum.

DIRECT EXAMINATION OF THE GASTRIC JUICE

A NEW FUNCTIONAL TEST

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For a study of gastric conditions we are able to avail ourselves of test meals, such as the Boas-Ewald, Riegel-Leube or Boas, which give a certain amount of evidence regarding both the motor and the secretary functions of the stomach. But if we are concerned with gastric motility alone, this can be examined more easily and accurately by roentgenographic methods, while in practice it has been demonstrated that the test meal method affords only partial information concerning irregularities in gastric secretion. In making use of the test meal we can only obtain a mixture of food and stomach secretions, never the pure gastric juice alone. And because of this dilution and chemical admixture with the ingested food, it is impossible to make any accurate estimate as to the precise amount of secretion given off, this difficulty being still further enhanced by the fact of its fractional withdrawal.

Normally, the outpouring of gastric secretion takes place only when stimulated by the ingestion of food, and examination of this secretion has been undertaken when it had previously been induced by the administration of the test meal. The original Ewald and Leube tests emptied the stomach at the height of digestion. Examination of the secretion from the fasting stomach was not undertaken except in suspected states of retention or hypersecretion.

DIRECT EXAMINATION OF THE GASTRIC JUICE

With the advent of the Rehfuss tube, however, we have a means that enables us to make examination of the gastric content by a fractional method, and it becomes possible to make routine study of the fasting stomach, investigating the gastric juice—its secretion, concentration and amount, as well as its influence, psychic and otherwise—very much as may be done in animal experimentation by means of fistulas or the Pawlow pouch.

TECHNIC

The Rehfuss tube is introduced into the fasting stomach, and its content withdrawn by means of a perfectly tight syringe. The tube is then left in place. As the gastric juice accumulates it is withdrawn at predetermined intervals—three, five, ten or fifteen minutes—and the quantity and total acidity of each portion separately determined. Any special examination, microscopic or otherwise, can be performed at the same time on any or all of these samples.

So far as my examination of the literature has gone, no such test has heretofore been recommended, either to complete the functional food tests in common use, or as a substitute for them, when it is desirable to obtain pure gastric secretion, unadulterated by food, a procedure which, as has been pointed out by Compton, would open up a wide field of study in relation to gastric function.

When the Rehfuss tube remains in the stomach the presence of its tip will excite and maintain the process of gastric secretion in those persons whose stomachs are in a state of hyperexcitability; in normal stomachs this mechanical stimulus will produce no secretion whatever. The observations reported in this article were made during the last eight months on some fifty patients, in the majority of whom there was a condition of gastric hypersecretion. Some 200 separate examinations of the fasting stomach content were made on these patients, the single determinations on the withdrawn samples numbering more than 1,000.

These cases can be roughly divided into two groups: (1) those in which no hypersecretion exists: in these there is no free gastric juice—or at most from 5 to 10 cc. of mucus showing hypacidity—and there is no drainage from the tube, no matter how long it is left in place, its tip failing to stimulate the secretory mechanism of the fasting stomach; (2) those in which hypersecretion is present. In these the introduction of the tube produces an outpouring of gastric secretion when the stomach has received no food for an extended period. Examination should be carried out after an alimentary rest of from twelve to fourteen hours, preferably in the early morning. The patients in this group comprise those suffering not only from primary hyperacidity or hypersecretion, but also from peptic ulcer of the stomach or duodenum, hypersecretion with anacidity, and all other diseases that are accompanied by secondary disturbances of gastric secretion. As to the incidence of gastric hypersecretion, I may quote the statement of Einhorn: "In varying conditions other than gastroduodenal ulcers, perhaps nine out of ten exhibit signs of this secretory anomaly," although this estimate seems to me somewhat high.

SIGNIFICANCE OF SECRETORY DISORDERS

The significance of acidity of the gastric juice, or of the gastric content as a whole, may be evaluated from different points of view. Though anacidity or achylia is one of the most significant indications of gastric cancer, we know that it may be encountered in other morbid conditions, not only of the stomach but elsewhere in the organism, or even under normal conditions. When peptic ulcer exists hyperacidity and hypersecretion may accompany it, but, again, both these manifestations may be entirely lacking with peptic ulcer while, on the other hand, they may appear in connection with other morbid conditions or even be

present in otherwise normal health. In the normal person, too, there is often a wide divergence in the character of the stomach secretions obtained on different occasions, and this is even more true of persons out of health from any cause whatsoever. Therefore, there are no secretory findings absolutely pathognostic of any disease. If we take all these considerations into account it would hardly seem worth while to undertake any examination of the gastric juice, as the interpretation of the findings is subject to so many limitations. I say seem, for these limitations have been well characterized by Rehfuss and Hawk,[1] when they say, "Let us realize here and now with gastric analysis, as with X-ray, that neither lies, but it is our interpretation which is faulty." Our interpretation has been faulty in the past, but not lately, because we have

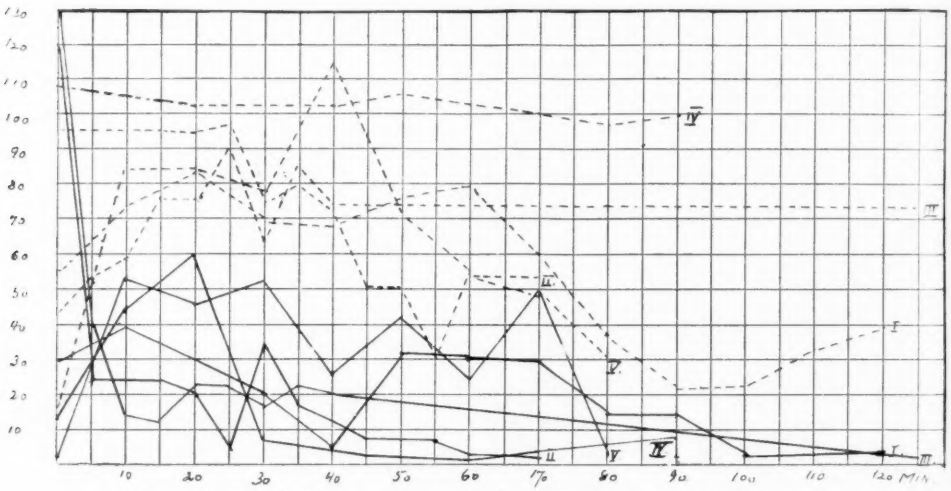

Chart 1.—Gastric juice on fasting and after aspiration in five minute intervals: Functional test at five different times, at about two day intervals, in B. R., a man, aged 56, with ulcer of the duodenum of twenty years' duration, with severe recurrences. Broken line: total acidity; solid line: gastric juice (cubic centimeters).

never obtained the gastric juice in unadulterated form; if we can now obtain the secretion in such a form that we are able to interpret it correctly, it certainly seems well worth while to undertake the labor involved in making accurate analyses.

The need for such study is at once apparent when we consider the wide divergence of opinion regarding all aspects of gastric analysis.

1. Rehfuss, M. E., and Hawk, P. B.: A Consideration of the Gastric Test Meal from Experimental Data, Tr. Twenty-third Ann. Meeting Am. Gastro-Enterol. A., May 3-4, 1920.

Earlier investigators asserted that between meals the stomach remained empty or at the most contained but a few cubic centimeters of clear gastric juice, showing perhaps a slight acidity. Rehfuss and Hawk, on the other hand, consider as an average normal finding in the fasting stomach about 50 cc. of fluid with free hydrochloric acid and a total acidity of from 30 to 50. My own experience is in accord with the earlier observations. Again, hypersecretion is generally cited as an almost pathognomonic sign of ulcer in the stomach or duodenum, yet Einhorn, in a number of conditions other than peptic ulcer found hypersecretion in 90 per cent. When no basic principles uniformly stated and accepted exist, how can we hope to establish any sound or practical clinical procedure?

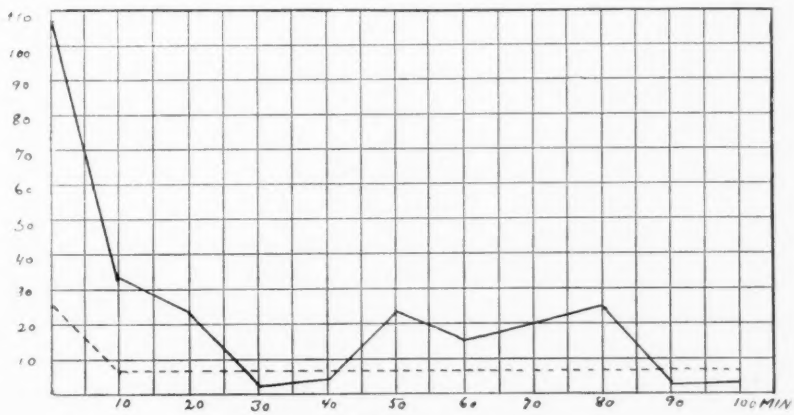

Chart 2.—Gastric juice on fasting and after ten minute intervals in H. S., a man, aged 54, with a tentative diagnosis of carcinoma ventriculi; hypersecretion and anacidity. Symptoms had been present for the last six years, and had been worse for the last six months. Free hydrochloric acid on fasting was 8; later it was always missing. Broken line: total acidity; solid line: gastric juice (cubic centimeters).

Some time before I elaborated this procedure, another method was adopted by Garbat,[2] while engaged in experimental work in Jacob Kaufman's service. After instituting duodenal alimentation, he observed an outpouring of gastric secretion analogous to that set up by the entry of food into the stomach, the secretion remaining in the stomach so long as there was any food in the duodenum. In other words, a definite cycle of gastric secretion took place, which was characteristic of

2. Garbat, A. L.: Gastric Secretion in Response to Duodenal Feeding, Arch. Int. Med. **32**:771-778 (Nov.) 1923; A New Method for Studying Pure Gastric Secretion, Am. J. M. Sc. **169**:687 (May) 1925; Treatment of Gastric Ulcer by the Method of Duodenal Alimentation, J. A. M. A. **84**:1992-1994 (June 27) 1925.

the individual's peculiar make-up, as has been especially emphasized by Kaufman, even when no food actually entered the stomach cavity or, as I have been able to demonstrate, when the stimulus to outpouring of secretion was due to the presence of the tube in the stomach. Rehfuss thought the material of which the tip was made, whether metal or rubber, was of importance, but Einhorn has pointed out that this is of no significance. It is certain that the tube does not induce the secretion. It merely increases its amount and maintains it, because in these cases of hypersecretion, the process is continuous and spontaneous.

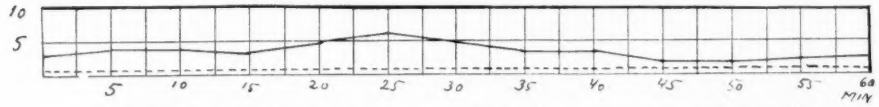

Chart 3.—Gastric juice on fasting and after aspiration in five minute intervals in S. K., a woman, aged 26, with gastric neurosis. All samples showed anacidity; the gastric juice was of thick, glassy, mucous quality. Broken line: total acidity; solid line: gastric juice (cubic centimeters).

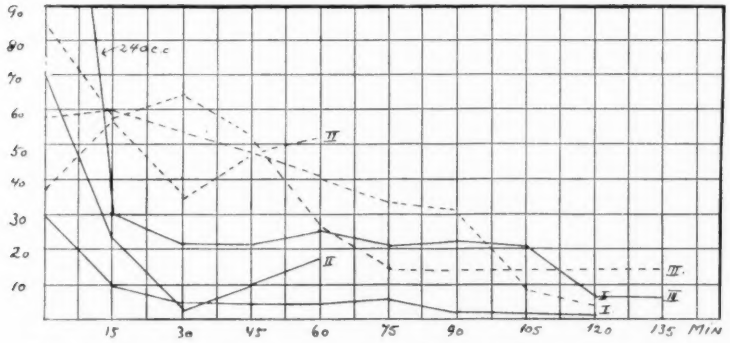

Chart 4.—Gastric juice on fasting and after aspiration in fifteen minute intervals in F. H., a woman, aged 34, with a moderately severe case of duodenal ulcer. Two parallel tests were performed at a one day interval. In the third, a tube was inserted two hours after a Ewald-Boas test breakfast; the first four portions withdrawn still contained residual meal; all the other samples were clear gastric juice. Broken line: total acidity; solid line: gastric juice (cubic centimeters).

While both Garbat's method and my own provide for obtaining unadulaterated gastric juice for analysis or other purposes, and I have no wish to minimize or deny the scientific value of Garbat's method, I still feel that my own is worthy of greater consideration, if for no other reason than its extremely easy application, its performance being even more simple than the administration and examination of a test breakfast.

PECULIARITIES OF SECRETED GASTRIC JUICE

While it is evident that it will not be possible to withdraw all the gastric juice entering the stomach, as some is bound to escape through the pylorus, we must not make too great an allowance for such discrepancies, and there is no doubt that the quantity withdrawn gives an excellent approximation to the amount actually secreted.

If the tube introduced into the fasting stomach does not produce any secretion it is not likely to do so if allowed to remain in place. If the stomach contains free gastric juice, the tube will give a more or less continuous return, this being to some extent proportional to the quantity and concentration of the gastric juice which was present in the fasting stomach. If there is any irritative secretory disturbance in the viscus under examination, the tube left in place will after a few minutes show the start of a typical secretion curve, and this curve will be more characteristic and convincing than were the observations made when the fasting stomach was first entered.

Usually the quantity and concentration of the gastric juice will be greatest some five or ten minutes after the introduction of the tube. When the mechanism of secretion has been at work for some thirty to forty minutes there will be a noticeable decrease in the amount outpoured; this is an expression of exhaustion. Decrease in concentration and in quantity may occur simultaneously, or follow one after the other, but the curve always shows marked individual variation, and even in the same subject under identical conditions, there may be differences all the way to 100 per cent in acidity values, and even more than 100 per cent in the quantity of gastric juice secreted. During the phase of exhaustion, the material withdrawn may contain mucus or duodenal secretion, with a visible admixture of regurgitated bile. As a rule, this depressed or inhibited phase will last from five to fifteen minutes, after which the process of secretion will be resumed at approximately the previous rate. After the lapse of thirty to sixty minutes, another longer and more lasting phase of exhaustion will set in; this sometimes continues for many hours. During the night's rest gastric secretion is relatively inhibited, so that often the amount found in the stomach in the morning will be relatively much less than one would expect to find in correspondence to the height of secretion during the test. It is understandable also that the secretion curve should drop after being exaggerated by stimulation, for otherwise there would quickly be an imbalance in the chemical reaction of blood and tissues, a rapid exhaustion of the system and an enormous alkalosis of the blood, which would be incompatible with life.

For example, in a severe case of hypersecretion due to chronic duodenal ulcer, 170 cc. of gastric juice was obtained from the fasting

stomach; at three minutes intervals, with a total acidity of 80, the average amount withdrawn at one time being 30 cc. Thus, in the first half-hour there was a loss of 300 cc. of gastric juice, with a concentration of 80. Had secretion continued at this level for twenty-four hours, there would have been a loss of 15 liters of gastric juice, which would have entailed total dechloruration of the system.

The ingestion of food acts as a chemical stimulus to increased secretion, and also as a source of further secretion. This irritative secretory condition is responsible for a more or less continuous process, often enduring for weeks or even months, during which relief is only afforded by incessant or recurring vomiting. As the food intake is deficient in spices, especially in salt, it is obvious that such a high degree of hypersecretion could not possibly persist for any length of time.

OBJECTIONS TO THERAPEUTIC DUODENAL FEEDING

Duodenal feeding has recently attained much popularity as a means of resting the stomach or duodenum when ulcer is present. I feel, however, that the difficulty of keeping the duodenal tube in place for the long period of time necessary is a very serious drawback to this procedure, and agree with Arthur L. Holland when he says: "Notwithstanding the many favorable reports of duodenal feeding, I believe that the principle is wrong, that whatever is gained in resting of the secretory apparatus of the stomach is lost in the spasm and irritation the tube must constantly excite." In addition to the loss of gastric digestion and the psychic reaction which attach to this method and are mentioned by Holland, I would point out the loss of the food's acid binding power—peculiarly true of proteins—which is so advantageously employed in Lenhartz's diet. All these are factors mitigating against the employment of duodenal feeding.

Should this method of alimentation be adopted, not only is the acid binding power of the proteins lost, but also—and notwithstanding the general views based on the results of this test—the secretory apparatus instead of being put at rest is kept in a hyperactive state, temporarily at least, except during the phase of exhaustion. It may be objected that in duodenal alimentation the tip of the tube is in the duodenum, while in the method I am advocating, the tip does not pass through the pylorus. In answer to this in addition to the mechanical insult of the tube on the gastric mucosa I may cite the experiments of Garbat already quoted, that irritation in the duodenum and frequent gastric regurgitation are the threefold reason causing the mechanism of stomach secretion to become active, so that actually the stomach does not "rest" even when no food enters it.

Whatever the interrelationship between hyperacidity or hypersecretion and peptic ulcer may be, it is certain that their coincidence is not

merely accidental. It is rather a fairly regular condition and the wonderful results obtained following subtotal gastrectomy, when the hydrochloric acid disappears and there is no recurrence of ulceration, as Berg [3] has so especially emphasized, prove that the relationship between these pathologic conditions is a close one. If the gastric mucosa is kept in a condition of irritation by the permanent presence of the duodenal tube, thereby provoking and increasing gastric secretion, it is evident that it will favor the development and persistence of gastric ulcer, rather than aid in abolishing it. There has been practically no contradiction of the results reported from the studies of Portis and Portis,[4] wherein it was shown that "neutralization plays the most important rôle in explaining the absence of free hydrochloric acid, observed experimentally and clinically in the gastric secretion after subtotal gastrectomy," and this is because the absence of free hydrochloric acid is associated with high combined acidity.

CONCLUSIONS

1. The Rehfuss tube may be introduced into the fasting stomach and left there to induce gastric secretion, which can then be fractionally withdrawn.

2. The examination and study of gastric juice unmixed with food can thus be made possible, and the results used to complete the test meal examinations, or as a substitute for them as the method gives a more exact account of the concentration and quantity of gastric juice secreted.

3. Two types of gastric secretion are discriminated, that of the normal stomach and that of the stomach affected with irritative secretory disturbance.

4. In the normal stomach after fasting, even when the tube is left in place from ten to sixty or more minutes after introduction, no gastric secretion can be obtained, either by drainage or suction.

5. In the stomach affected by irritative secretory disturbance, there is hypersecretion on fasting, usually with hyperacidity, though normal acidity and occasionally anacidity may be noted. After a three to fifteen minute interval similar gastric juice may be obtained by suction. Occasionally, hypersecretion with anacidity is found in cases showing free hydrochloric acid and possibly later hyperacidity after the customary test meals.

6. The amount of gastric juice secreted immediately after the insertion of the tube may be several times greater than the *relative* quantity

3. Berg, A. A.: Radical Cure of the Gastric and Duodenal Ulcer, read at the New York Academy of Medicine before the American-Hungarian Medical Association, Feb. 16, 1926.

4. Portis, S. A., and Portis, Bernard: Effects of Subtotal Gastrectomy on Secretion, J. A. M. A. **86**:836 (March 20) 1926.

accumulated during the night's rest. The acid concentration is, as a rule, much less increased.

7. From one-half an hour to one hour after the tube is inserted, a phase of exhaustion of the mechanism of gastric secretion will intervene, the quantity and concentration of the gastric juice being temporarily markedly reduced.

8. This phase of exhaustion is characterized by a protective mechanism which produces a secretion with heavy admixture of mucus and regurgitated gall, and also containing duodenal secretion.

9. The first phase of exhaustion endures from ten to fifteen minutes. After an active interval of thirty to sixty minutes, there will be a second period of exhaustion, often lasting many hours.

10. Information concerning the motility of the stomach can be obtained through the use of this test, at the same time the gastric juice is being withdrawn for study. For this purpose it should be performed when the stomach has just been emptied after the administration of a test meal, e. g., two hours after the test breakfast.

CAPILLARY PERMEABILITY AND THE INFLAMMATORY INDEX OF THE SKIN IN THE NORMAL PERSON AS DETERMINED BY THE BLISTER*

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In the recent advances made in the study of the capillaries, methods of visualization have played the larger rôle, with the result that most investigators have studied alterations in appearance rather than function, and if the latter, only indirectly. Much of the work has taken origin in the careful work of Otfried Müller[1] and of Krogh.[2] Stricker,[3] Hooker[4] and Ebbecke[5] have devoted much time to a study of the functional alteration of the capillary and Ebbecke particularly to the bio-electrical changes that accompany or initiate changes in function. Ebbecke's work can be correlated with the clinicopathologic studies of the Kraus[6] school on the ionic equilibrium of the body, particularly the calcium and potassium balance.

We have heretofore been accustomed to think of the capillary system and its functional control in terms of the vasomotor nervous mechanism and have come to confuse the reaction of the musculature of the arteriole with the presumptive reaction of the capillary wall. Indeed, an independent dilatation and contraction of the capillary has until recently been regarded as improbable, or merely of academic interest.

The single endothelial cell (disregarding for the moment any adventital element, such as the Rouget cell) of the capillary wall has the inherent protoplasmic reactivity of any other cell. Its surface membrane is the seat of the same bio-electrical, ionic and physical changes that accompany changes in reactivity in a free living ameboid cell. Stimulation involves lessened turgor, lowered surface tension, greater permeability, lowered surface charge, lessened calcium and increased

* From the department of pathology, University of Illinois College of Medicine.

1. Müller, Otfried: Die Kapillaren der menschlichen Korperoberfläche, Stuttgart, 1923.

2. Krogh, August: Anatomy and Physiology of the Capillaries, Yale University Press, 1922.

3. Stricker: Vorlesungen über die allgemeine und experimentelle Pathologie, Vienna, 1883.

4. Hooker, D. R.: Physiol. Rev. **1**:112 (Jan.) 1921.

5. Ebbecke, U.: Klin. Wchnschr. **2**:1725 (Sept. 17) 1925.

6. Kraus, F., and Zondek, S. G.: Klin. Wchnschr. **1**:996 (May 13); 1773 (Sept. 2) 1922. Zondek, S. G.: Ibid. **4**:905 (May 7) 1925.

potassium content. And with endothelium making up a hollow tube, stimulation will result in the capillary becoming more distensible and the lumen larger.

Such a change may be brought about by a nerve impulse—and the demonstration of nerve fibers to the capillary walls seems well established—but more likely it is due to direct effects on the cell surfaces by alterations in the blood plasma, or of the tissues of the region supplied by the capillary. Fundamentally such changes are, of course, ionic and bioelectrical, i. e., changes in the hydrogen ion concentration and in the calcium-potassium balance.

Alterations brought about by nerve impulses or as the result of hormone changes are also brought about by ionic rearrangement. It has been repeatedly demonstrated that the nerve impulse will elicit a response depending in its character on the ionic equilibrium obtaining at the time the impulse reaches the cell. Experiments have been reported which show that the effect of the hormones likewise depends in a large measure on the ionic equilibrium existing at the cell surface.

Evidence can be cited at length from the work of Lillie, Osterhaut, Embden and Gildermeister, to mention only a few, that the cell can respond to an alteration of external conditions in one of two ways. The cell membrane may become *more permeable* (we usually think of this modification of the state of the cell as stimulation) and accompanying this change will have enhanced oxidation, increased excretion of lactic acid, phosphates and calcium; it will take up more potassium, the surface charge will be lessened, the surface tension reduced, the cell turgor lessened, ameboid motion and phagocytosis will be enhanced. It may become *less permeable* (we regard this in specialized cells as a refractory period, in a general sense as a period of rest), will contain more calcium and less potassium, will have a higher surface potential, with greater surface tension, greater turgor and less ameboid motion. Either change may take place as a reaction to environmental alterations and in this sense we may regard the effect of a stimulus as one that will increase or retard activity of the cell. This is perhaps contrary to the usual physiologic or pathologic concept, and yet we believe on analysis will be found to be logical.

If we now examine the factors that, when acting directly, alter the cell in one direction or the other we find approximately those given in table 1.

Our endothelial cell may respond to any of these agents, becoming either more or less permeable as the case may be. Largely it will be a local control as a result of environmental changes of the surrounding tissue. But it may be hormonal and in some instances autonomic, always bearing in mind that many of the autonomic agents also act directly on the endothelial cell itself, without reference to neurocellular junction.

Let us examine for a moment the contractile mechanism. That at best is rudimentary and incomplete. The Rouget cell is relatively undifferentiated—pathologists frequently group the tissue with reticulothelium (Marchand). These cells seem definitely under autonomic control, contracting on stimulation of the local sympathetics and with epinephrine application. They correspond in general to the innervation of the arterioles.

This muscular mechanism has been superimposed on the more primitive system and its nervous control, too, is a later addition to the mechanism of regulation. Consequently direct stimulation of the endothelium (with increased permeability and dilatation of the capillary) may occur simultaneously with stimulation of the musculature through a nervous influence, so that we will have effects which in many respects are seemingly antagonistic. Usually, however, the capillary becomes permeable with agents that act on the parasympathetic system and so cause capillary dilatation and increased permeability as well as arteriole relaxation.

TABLE 1.—*Factors That Alter Cell*

Increased Permeability	Diminished Permeability
1. Parathyroid, thyroid (?), sex hormone (menstruation)	1. Epinephrine, pituitary extract, insulin (?)
2. Pilocarpine, muscarine, choline, peptone, paraphenylendiamine, physostigmine, etc.	2. Picrotoxin, strychnine, santonin (because of mobilization of epinephrine)
3. Caffeine, theophylline, etc.	
4. Many of the narcotics, including alcohol, veronal, etc.	
5. Increased hydrogen ion concentration	3. Diminished hydrogen ion concentration
6. Increased temperature	4. Diminished temperature
7. Potassium effects	5. Calcium effects

In previous articles [7] we have studied capillary permeability in the experimental animal by means of thoracic duct incannulation. These studies showed the relatively rapid reversibility of membrane changes—period of time by a reversal to impermeability—with later further fluctuations. We were able to demonstrate the increase in permeability in shock from peptone and anaphylaxis, as a result of the primary effect of tuberculin and of arsenic, and the decrease in permeability with epinephrine and pituitary extract and as a secondary phenomenon following tuberculin and arsenic. We then studied the chemical changes in the lymph that accompany these alterations. The relation to the autonomic nervous system has been discussed by Müller and one of us.[8]

It seemed desirable to us to examine the permeability of capillaries of normal persons as well as under various pathologic conditions, and in

7. Petersen, W. F.; Levinson, S. A., and Hughes, T. P.: J. Immunol. **8**:323 (Sept.) 1923.

8. Müller and Petersen: Klin. Wchnschr. **5**:2, 1926.

considering the possible methods for such a study we finally have adopted the simple expedient of making a cantharides blister and determining the ratio of protein that comes through into the blister as compared to the protein concentration of the serum.

Blister formation in patients has been used by a number of investigators in biochemical or serologic problems. As far as we can determine the only one who has worked with the blister method for the purpose that we have in view has been Gänsslen.[9] Otfried Müller and his associates have been interested chiefly in the microscopic study of the capillary in the living subject and in order to obtain some information as

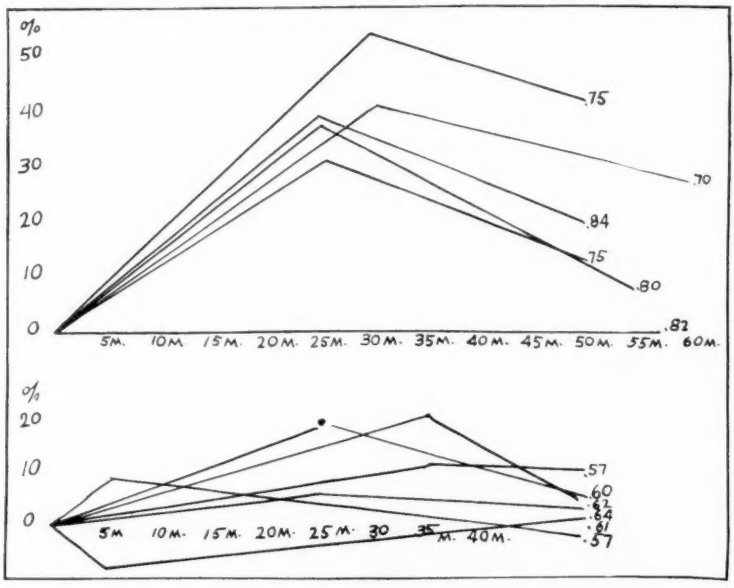

Chart 1.—Effect of 5 minims of epinephrine (1 : 1,000) subcutaneously, expressed as pulse rate times pressure in percentage of normal; upper: group 1, permeable; lower: group 2, impermeable.

to the functional capacity, Müller suggested the possibility that the blister might be of use. Gänsslen used cantharides plaster applied to the outer surface of the ankle. He placed six small plasters on the skin and he had them removed at intervals of two hours. On observing the blister formation the following day he would note the length of time that it had required for the plaster to draw a blister, and this was then noted as the blister time. With his plaster and method, the average normal time was

9. Gännslen, M., and Müller, O.: München. med. Wchnschr. **69**:263 (Feb. 24) 1922. Gännslen, M.: Ibid. **69**:1176 (Aug. 11) 1922.

approximately twelve hours. Much shortening was noted in the vascular neuroses, in exophthalmic goiter, and in severe diseases associated with hemorrhagic diathesis. He determined the amount of protein in some of the blisters but made no systematic study of permeability, although Müller in his introduction mentions the desirability of such investigation. Gännslen later studied the relative amount of nonprotein nitrogen and sugar in the blister fluid and serum in cases of nephritis.[10]

The dermatologists have studied blister formation and Weidenfels [11] in particular has devoted much attention to the subject. He concludes that the fluid is drawn from the lymph spaces. Whether from lymph spaces or directly through capillary wall is, however, for the purpose that we have in mind, immaterial. In either instance the fluid must have

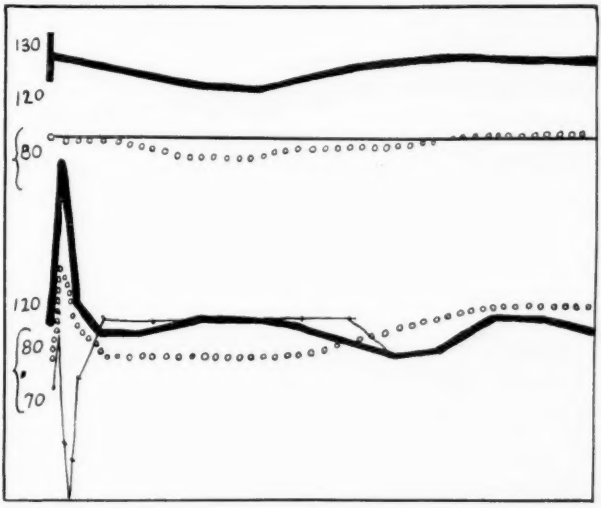

Chart 2.—Upper: effect of 5 minims of epinephrine subcutaneously on student 12; ratio, 61; lower: effect of 1 minim of epinephrine intravenously; heavy line, systolic, dotted line, diastolic blood pressure; light line, pulse rate.

passed through an endothelial wall and have been modified in its protein concentration by so doing. Gännslen noted that it was immaterial by what means the blister was produced and regarded the cantharides plaster as the most useful. Cantharides being lipoid soluble enters the skin readily and probably produces its effect in two ways, on the sensory nerve ending and directly on the capillary wall.

The stimulation of the sensory nerve ending apparently is transmitted directly as an axone reflex to the adjacent skin arteriole, for it has been

10. Gännslen, M.: München. med. Wchnschr. **70**:1271 (Oct. 12) 1921.
11. Weidenfels, quoted by Pulay: Eczem und Urticaria, Vienna, 1925.

repeatedly demonstrated that such reflexes may take place with total severance from the central nervous system (Bayless, Bruce, Spiess) and Bruce [12] has furthermore shown that when the sensory ending is anesthetized, inflammatory agents that act solely through the nervous pathway are no longer able to induce inflammation.

Cantharides acts also as a specific capillary irritant without altering the rest of the protoplasmic elements to any great extent. It is this property that causes it to produce an inflammatory reaction even when the sensory effects are blocked.

METHOD

Blister Time.—We have used a common commercial grade of cantharides plaster (B. and B.). This has been applied at a definite time (4 a. m. for patients, 8 a. m. for student controls) in the morning, the plaster left on for six hours, then removed and the area observed at

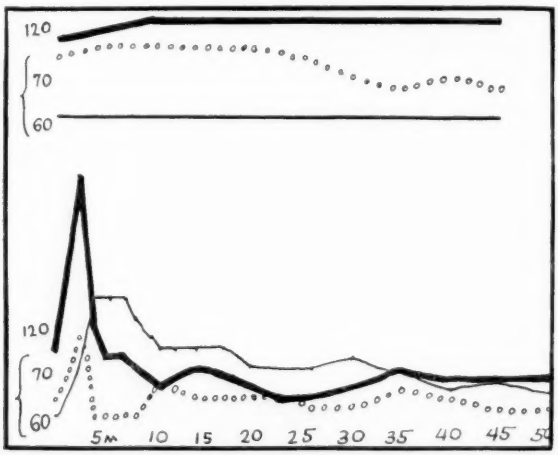

Chart 3.—Upper: effect of 5 minims of epinephrine subcutaneously on student 65; ratio, 82; lower: effect of 4 minims of epinephrine intravenously; heavy line, systolic, dotted line, diastolic blood pressure; light line, pulse rate; *x*, time of injection.

intervals for blister formation. The time when the first definite elevation appears has been taken as the blister time. In some patients the blister time is very short. A severe burning sensation usually brings the plaster to the attention of the patient and in these cases the plaster has usually been removed at an earlier time.

The plaster has been uniformly applied to the inner surface of the forearm just below the elbow.

12. Bruce: Quart. J. Exper. Physiol. **6**:339, 1913.

Permeability Ratio.—Sufficient fluid having collected, the blister is immediately evacuated (if fluid remains for any length of time in the blister, its protein content diminishes, probably because of proteolysis) and at the same time a blood sample is collected in a Wright capsule from the ear lobe. Disregarding fibrin, the two samples (blister fluid and serum) are now examined by means of the refractometer for their protein content. The readings for the blister fluid are made according to the Reiss exudate table, those for the serum from the regular serum table. The ratio $\frac{\text{percentage of blister protein}}{\text{percentage of serum protein}}$ gives us our permeability ratio.

Inflammatory Index.—If we now wish to express the relative inflammatory response of the individual to the particular irritant in question we use the following coefficient $\frac{\text{permeability ratio}}{\text{blister time}}$. For example, blister protein is determined as 4 per cent, the serum protein as 6 per cent. The permeability ratio is 66. It takes eight hours to form the blister. $\frac{66}{8} = 8.2 =$ inflammatory index.

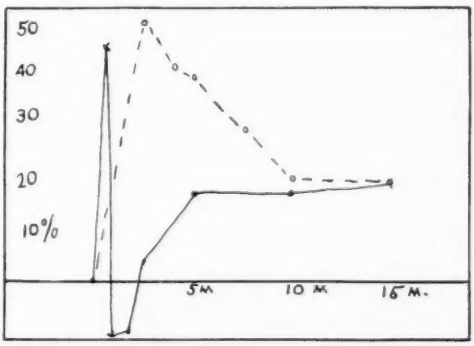

Chart 4.—Solid line: effect of 1 minim of 1:1,000 epinephrine on student 12; broken line: effect of 4 minims of 1:1,000 epinephrine on student 65, in terms of pulse rate times systolic pressure in percentage of increase from normal before intravenous injection.

We need not emphasize that it is essential to work under uniform conditions. Repeated control observations in the same persons under such circumstances have given us quite comparable results, the variation being from 2 to 4 per cent. It is essential, however, that a uniform plaster be employed.

These two coefficients give us direct information about two more or less distinct phenomena. The index of permeability indicates the *actual degree of response of the capillary endothelium to a direct stimulus* (in this case the cantharides). It has no direct relation to the autonomic nervous system except so far as the underlying endocrine and ionic equilibrium affect both protoplasm and autonomic nervous tissue.

The inflammatory index includes the effect of the autonomic tonus. If a blister forms rapidly we have every reason to believe that the axone reflex has produced a prompt relaxation of the arteriole musculature because the tonus of the sympathetic system is low; conversely, the delayed blister indicates that the relative sympathetic tonus is high and that the spasm of the arteriole musculature is the factor that delays the transudation of fluid from a capillary that may be relatively permeable. Usually increase in capillary permeability goes hand in hand with diminution of the sympathetic tonus, but not always.[13]

Normal Men.—Before proceeding to a study of patients we have taken advantage of the opportunity of studying normal young men and women, for which purpose we have had the voluntary cooperation of some seventy students.

We have examined, in addition to their blister time and permeability, the following in all or in smaller groups of students: Urine, blood pressure, blood chemistry, basal metabolic rate, the epinephrine reaction, the reaction to roentgen rays, and the tuberculin reaction. In addition we obtained a history of the student and a roentgenogram of the thorax.

The following presentation details the relation of some of these observations to the relative permeability and inflammatory reaction of a group of sixty-six of such students (men in the age group of 22-25). In table 2 the material has been grouped in the order of the relative permeability of the students, in table 3, in the order of the inflammatory index.

As shown in the second table, the permeability varies from 57 to 84, and the table has been divided into two portions, *A*, low permeability; *B*, high permeability. The average for the whole group is 68, which has been used as the dividing line.

The inflammatory index varies from 3.5 to 18.5, the average for the entire group being 10.5. This table also has been divided into two groups, with thirty-four students in the first group and thirty-two in the second (to correspond to the first table).

ANALYSIS OF RESULTS

Clinical Examination.—Presumably the students were all normal. On examination it will be seen, however, that there were several exceptions.

Students 32 and 34 were found on roentgen-ray examination to have evidences of active tuberculosis. The lesion in student 32 was associated with obvious constitutional effects.

13. We have stressed the tonus of the arteriole in producing a long or short blister time and in relation to the inflammatory index merely for the sake of simplicity. The subject is, of course, much more complex and it might indeed be more proper to speak of the tonus of the whole tissue. Landerer many years ago studied just such a relation of the connective tissue elements to the formation of an edema.

TABLE 2.—*Normal Student Group Arranged According to Relative Capillary Permeability*

				A				
No.	Permeability Ratio	Clinical Diagnosis	University Athletics	Sensitization	History of Clinical Tuberculosis	History of Family Tuberculosis	Roentgen-Ray Diagnosis	Urinary Changes
1	0.57	Psoriasis	—	—	—	—	—	
2	0.57	—	—	—	—	Sister active	1. Ghon†; healed pulmonary	
3	0.57	—	Yes	Hay-fever	—	—	Hilum	
4	0.57	—	—	Urticaria	—	—	Hilum	
5	0.57	—	Yes	—	—	Brother died	Hilum	
6	0.57	—	—	—	—	—	Hilum	
7	0.59	—	Yes	Horse serum	—	—	Hilum	
8	0.59	—	—	—	Yes (kidney)	Entire family	2. Marked hilum shadows	
9	0.60	—	—	—	—	—	—	
10	0.60	—	—	—	?	?	3. Marked calcification of costal cartilages	Albumin and casts
11	0.61	—	Yes	—	—	—	Normal	
12	0.61	—	Yes	—	—	—	Hilum somewhat increased	
13	0.61	—	—	—	—	Grandparents; uncle	4. Old healed pulmonary	
14	0.62	—	Yes	—	—	—	Hilum	
15	0.62	—	—	—	—	—	5. Old healed pulmonary	
16	0.63	—	—	—	—	—	Normal	
17	0.63	—	—	—	—	Father	6. Old healed pulmonary	
18	0.63	—	—	—	Yes	—	7. Old healed pulmonary	
19	0.63	—	—	—	—	—	8. Possibly old healed pulmonary	
20	0.63	—	Yes	—	—	—	Hilum	
21	0.64	—	—	—	—	—	Normal	
22	0.64	—	—	—	—	—	Marked hilum	
23	0.64	—	Yes	—	—	Yes	9. Old healed pulmonary	
24	0.65	—	—	—	—	—	Normal	
25	0.65	—	—	Horse serum	—	—	Increased hilum shadows	
26	0.65	—	—	—	—	—	Normal	
27	0.65	(During migraine)	—	—	?	Yes	Hilum	Albumin and casts
28	0.65	—	—	—	—	—	Hilum	
29	0.65	—	—	—	—	—	Hilum	
30	0.66	—	Yes	—	Yes	Brother	10. Old healed pulmonary	
31	0.66	—	—	—	—	—	Normal	Occasional casts
32	0.66	—	—	—	—	Uncle	11. Active right upper lobe	
33	0.67	—	—	—	—	—	Hilum	
34	0.67	—	—	—	—	—	12. Active right upper lobe	
			9	4	3	9	12	3

† Ghon tubercle—a healed primary lesion of the lung.

TABLE 2.—*Normal Student Group Arranged According to Relative Capillary Permeability* (Continued)

					B			
No.	Permeability Ratio	Clinical Diagnosis	University Athletics	Sensitization	History of Clinical Tuberculosis	History of Family Tuberculosis	Roentgen-Ray Diagnosis	Urinary Changes
35	0.68	—	—	—	—	—	Hilum	
36	0.68	—	—	—	—	—	Hilum	Albumin and casts
37	0.68	—	—	—	—	Yes	Hilum	
38	0.69	—	—	—	—	—	Hilum	
39	0.70	—	—	—	Once suspected	—	1. Ghon.; left lobe	Albumin (faint trace)
40	0.70	—	Yes	—	—	—	Hilum	
41	0.70	—	—	—	—	—	Normal	
42	0.70	—	—	—	—	Yes	Normal	
43	0.70	—	—	—	—	—	Marked hilum	
44	0.70	—	—	—	Yes	—	2. Healed upper right pulmonary	
45	0.71	—	—	—	—	—	3. Ghon.; left lobe; healed upper lobe; pulmonary	Albumin
46	0.72	—	—	—	—	—	Hilum	
47	0.72	—	—	—	—	—	Hilum	
48	0.72	—	—	—	—	—	Marked hilum; healed parenchyma (?)	
49	0.73	—	—	—	—	—	Moderate hilum	
50	0.73	—	—	—	—	—	Hilum	Occasional casts
51	0.73	—	—	—	—	—	Hilum	
52	0.74	—	—	—	—	—	Hilum	
53	0.74	—	—	—	—	—	Hilum	
54	0.74	—	—	Yes	—	—	Old adhesions; pleurisy (not tuberculous)	
55	0.74	Congenital ichthyosis (mild)	—	—	—	—	Hilum	
56	0.74	—	—	—	—	—	Marked hilum	
57	0.74	—	—	—	—	—	4. Old healed pulmonary	
58	0.75	—	—	—	—	—	Moderate hilum	
59	0.75	Duodenal ulcer	—	—	Glands of neck in childhood	—	5. Ghon.; moderate hilum	
60	0.76	—	—	—	—	—	Normal	
61	0.77	—	—	—	—	—	Hilum	
62	0.77	—	—	—	—	—	Hilum	Albumin and casts
63	0.79	—	—	—	—	—	6. Old healed parenchymal; right upper active ?	Casts (occasional polyuria)
64	0.80	Exophthalmic goiter (recovered)	—	—	—	—	7. Ghon.; left lobe	
65	0.82	Vagotonic	—	—	—	—	Hilum	
66	0.84	Neurovascular asthenia	—	—	—	—	Hilum	
			1	1	3	2	7	6

TABLE 3.—*Normal Student Group Arranged According to Inflammatory Index*

Student	Index	University Athletics	Sensitization	History of Clinical Tuberculosis	History of Family Tuberculosis	Roentgen-Ray Diagnosis of Tuberculosis	Influenza	Scarlet Fever	Diphtheria	Albumin and Casts
6	3.5	..	..	..	..	..	—	—	..	..
5	5.2	+	..	+	+	..	—	—	+	..
22	5.8	..	..	..	..	..	—	+	..	..
44	6.4	..	..	..	..	+	+	+	..	..
27	6.5	..	..	+	+	..	—	—	..	..
10	6.7	..	..	..	+	+	+	+	..	+
30	6.7	+	..	..	+	+	+	—	..	+
50	6.9	..	..	..	..	..	+	—	..	..
19	7.0	..	..	..	..	+	—	—	..	+
1	7.1	..	..	..	..	..	—	—	..	..
12	7.1	+	..	..	..	..	+	—	..	..
32	7.3	..	..	..	+	+	+	+	+	..
9	7.4	..	.	..	..	..	—	—	..	..
20	7.4	+	..	..	..	..	—	—	..	..
3	7.6	+	+	..	..	..	—	—	..	..
41	7.7	..	..	..	..	..	+	—	..	..
8	7.9	..	..	+	..	..	+	—	..	..
4	8.1	..	+	..	..	+	+	—	..	..
26	8.1	..	..	..	..	..	—	—	..	..
31	8.3	..	..	..	..	..	—	—	..	..
36	8.5	..	..	..	..	..	+	+	+	+
24	8.6	..	..	..	..	..	+	+	..	+
13	8.7	..	..	..	..	..	—	—	..	..
17	9.0	..	..	..	+	+	+	—	..	..
18	9.0	..	..	..	+	+	+	—	..	..
29	9.3	..	..	+	..	+	—	—	..	..
43	9.4	..	..	..	..	..	—	—	..	..
2	9.5	..	..	..	..	..	—	—	+	..
34	9.6	..	..	..	+	+	—	—	+	..
39	10.0	..	..	..	..	+	+	—	..	..
45	10.1	..	..	+	..	+	+	—	..	+
47	10.3	..	..	..	..	+	+	—	..	+
57	10.4	..	..	..	..	..	—	—	..	..
		..	..	..	..	+	—	—	+	..
		5	2		16		15	6	6	7
35	10.4	..	..	..	..	..	—	—	..	..
63	10.5	..	..	..	..	+	+	+	..	..
38	10.5	.	..	..	..	..	—	—	..	+
16	10.5	..	..	..	..	..	—	—	..	..
21	10.6	..	..	..	..	..	—	—	..	..
7	10.7	+	+	..	..	..	—	+	..	..
25	10.8	..	+	..	..	..	+	—	..	..
37	11.3	..	..	..	..	..	—	—	..	..
60	11.4	..	.	..	+	..	—	—	..	..
42	11.6	..	..	..	..	..	+	+	..	..
28	12.0	..	..	..	+	..	—	—	..	..
46	12.0	..	..	..	..	..	—	—	..	..
48	12.0	..	..	..	..	..	+	—	..	..
66	12.0	..	..	..	..	..	+	+	+	..
49	12.1	..	..	..	..	..	—	+	..	..
53	12.3	..	..	..	..	..	+	—	..	..
56	12.3	..	..	..	..	..	+	—	..	..
23	13.0	+	..	..	+	+	+	+	..	..
61	13.0	..	..	..	..	..	—	—	..	..
51	13.2	..	..	..	..	..	+	.	..	..
33	13.4	..	..	..	..	..	+	+	+	..
15	14.0	..	..	..	..	..	+	+	..	..
58	15.0	..	..	..	..	+	—	—	..	..
59	15.0	..	..	..	..	..	+	—	..	..
52	15.0	..	..	+	+	+	—	—	+	..
11	15.2	+	..	..	..	..	+	—	..	..
14	15.5	+	..	..	..	..	—	—	..	..
62	17.0	..	..	..	..	..	+	—	..	+
40	17.5	+	..	..	..	..	—	—	..	+
64	17.7	..	..	..	..	..	+	—	..	..
65	18.2	..	..	..	..	+	+	—	..	..
54	18.5	..	+	..	..	..	+	—	..	..
55	18.5	..	..	..	..	..	+	—	..	..
		..	..	..	..	..	—	—	..	..
		5	3		7		18	9	3	2

Student 8 had a tuberculous kidney removed two years before this examination. The nonprotein nitrogen of the blood was increased to 53.

Student 1 had a moderate amount of psoriasis; student 55 some ichthyosis.

Student 59 had a duodenal ulcer (roentgenologic confirmation of occasional symptoms).

Student 64 had an active exophthalmic goiter about one year before this experiment. He is now in a stage of inactivity, with basal metabolic rate of + 8. Some minor vasomotor disturbances remain.

Student 65 is the only one that can be classified as vagotonic. He has the lowest blood pressure, has a vagotonic epinephrine reaction, and perspires profusely on excitement.

Student 66 on examination is classified as a neurovascular asthenia patient, possibly on the basis of hyperthyroidism. The basal metabolic rate is + 8 and he has lost some weight during the last year.

Athletics.—We have limited the term to the activities of students who have made places on and have engaged in the strenuous athletic training of regular university teams (football, basketball, swimming, etc.). High school athletic activity has not been considered. It is apparent that with one exception all the athletes are in the group of relative impermeability. When we take into consideration the blister time (table 3), this difference is equalized. We can only interpret this as an indication that as a result of athletic activity—or because of the constitutional qualification involved in eligibility for athletes—these men have a capillary permeability that is lessened, but that the sympathetic tonus of the arterioles is unaltered.

Sensitization.—While the cases of sensitization are not many, the results are analogous to those for athletics. In the impermeable group are four out of the five who have a history of sensitization. Classified by the inflammatory index the difference vanishes. Of these students, student 3 comes of a family in which all members have hay-fever, as has this particular student. From the age of 10 to 12 he had asthma in addition to hay-fever.

Blood Pressure (table 4).—Analyzed on the basis of capillary permeability it is strikingly evident that diminished capillary permeability is associated with increased blood pressure. On the other hand, when we use the inflammatory index there is no evident relationship between the blood pressure and the degree of reaction, unless in the very slight increase in diastolic pressure with increase in inflammatory reaction. This, if confirmed by further work, can imply but one thing. The increased blood pressure is associated with lessening capillary permeability and not with the tonus of the arteriole. We are, of course, not dealing with pathologic conditions and we cannot state that any of these men will develop hypertension.

Albumin and Casts.—On the basis of permeability six of our nine students with albumin or casts in the urine belong in the permeable group, but examined on the basis of the inflammatory index this relationship is reversed and seven of the nine are in the group with low inflammatory reaction. The nine students have a permeability that

TABLE 4.—*Blood Pressures Arranged According to Inflammatory Index and Permeability*

Inflammatory Index	Blood Pressures		Permeability Ratio	Blood Pressures	Men
5.2	120/80	Average 12, 121/78	0.56	118/80	Average 12, 129/83
6.4	106/80		0.57	120/80, 130/80, 120/80, 148/90	
6.5	116/74				
6.7	118/78				
6.6	140/90		0.59	148/84, 134/92	
6.9	114/64		0.60	118/78, 134/92	
7.0	116/72		0.61	112/70, 134/90, 130/84	
7.1	118/80, 130/84				
7.3	116/68				
7.4	134/92, 128/80				
7.6	130/84	Average 19, 123/78	0.62	118/74	Average 19, 122/80
7.7	118/80		0.63	132/90, 140/100, 116/72, 128/80, 110/70	
7.9	134/92				
8.1	124/90, 120/80		0.64	130/90, 126/76	
8.3	120/78		0.65	120/80, 120/80, 116/74, 120/80, 110/78, 126/80	
8.5	140/90				
8.6	120/80				
8.7	134/90		0.66	120/78, 140/90, 116/68	
9.0	110/70, 140/100		0.67	118/76, 116/68	
9.3	126/80				
9.4	130/86				
9.5	120/80				
9.6	116/68				
10.0	116/78				
10.1	114/74				
10.3	120/90				
10.4	120/80				
10.4	118/80	Average 21, 124/81	0.68	118/80, 136/84, 140/90	Average 21, 121/80
10.5	118/85, 118/78, 132/90		0.69	118/76	
10.6	130/90		0.70	116/78, 128/90, 130/86, 118/80, 120/80, 106/80	
10.7	148/84				
10.8	120/80		0.71	114/74	
11.3	136/84		0.72	120/90, 115/70	
11.4	122/78		0.73	114/64, 138/90, 120/78	
11.6	120/80		0.74	128/80, 130/90, 120/85, 120/80, 120/80	
12.0	110/78, 115/70, 144/90				
12.1	138/90				
12.3	120/80, 128/80				
13.0	126/78, 118/80				
13.2	120/78				
13.4	118/76				
14.0	118/74				
15.0	118/70, 118/76	Average 8, 119/80	0.75	118/70, 118/76	Average 8, 120/80
15.2	112/70		0.76	122/78	
17.0	128/90		0.77	118/80, 128/90	
17.5	128/90		0.79	118/85	
17.7	(146/80)		0.80	(146/80 exophthalmic goiter)	
18.2	100/70		0.82	100/70	
18.5	120/80, 130/90		0.84	144/90	

averages 0.7 (normal 0.68) and a blister time that averages eight hours (average 7.1 hours). We regret that our series is not larger, but if we may draw any conclusions the material indicates that with evidences of kidney disturbance the capillaries have an increased permeability while the sympathetic tonus of the arterioles also is increased. We can readily

understand that such changes in the kidney would lead to an albuminuria. Jaffé has discussed the underlying microscopic changes in a recent article.[14]

Tuberculosis.—We have made a complete study of the student material to determine the relative amount of tuberculous infection—by history of familial contact, by evidences of past clinical activity and by a roentgenologic examination. Arranged by permeability it will be noted that of the impermeable group fourteen have either a distinct family history, a clinical history of past activity or a roentgen-ray diagnosis of parenchymal involvement (hilum tuberculosis disregarded). There are nine such cases in the permeable group. This difference is accentuated in the examination on the basis of inflammatory index, in which we find sixteen in the first group and only seven in the second group. Two of the students had active lesions and one was of doubtful activity roentgenologically.

We are of the opinion that the increased amount of tuberculous infection that has been overcome by the students in this group has resulted in a modification of the tissue so that there is less permeability and increased sympathetic tonus of the arterioles. The average blister time for the tuberculous cases was 7.4 hours (normal 7.1 hours). We shall comment on this relation in detail later.

Other Infectious Diseases.—When we turn to other infections, the relation of the permeability to influenza morbidity is of some interest (table 5). Exactly 50 per cent of the students report that they have had influenza at some time since 1918. The group of low permeability have had approximately half as much as those in the group with higher permeability. In the case of scarlet fever (fifteen cases) the permeable group also contained more cases, while diphtheria and typhoid were about evenly divided.

Arranged on the basis of inflammatory reaction the relative influenza morbidity for the groups is 44 and 56 per cent (table 2). There seems some definite relation between morbidity and permeability. In view of the clinical experience that both influenza as well as scarlet fever are apt to injure the endothelial system, the logical interpretation would seem to be that these infections have left the endothelium in a more labile state than normally. The other possibility that we must consider is that the impermeable person is less susceptible to the infection, for presumably the opportunity for infection has been uniform. That such a possibility exists might be inferred from the influenza statistics which show the relative immunity of persons in the tuberculosis sanatoriums during the recent pandemic. Patients with tuberculosis (chronic), as will be demonstrated later, are among the relatively impermeable group.

14. Jaffé, R. H.: Am. J. M. Sc. **169**:88 (Jan.) 1925.

REACTION TO EPINEPHRINE

From the group we next selected men of low and high permeability (six of each) and injected 5 mm. of epinephrine (1:1,000) subcutaneously. The pulse rate and blood pressure were recorded every five minutes for approximately one hour. The pulse rate times the blood pressure was calculated, preinjection figures taken as 100 per cent and changes from the normal computed in percentage of the normal figure. In chart 1 the time of maximum alteration for the two groups of students has been charted. The permeability index of the students is noted at the end of each individual curve.

TABLE 5.—*Relation of Permeability Ratio to Influenza Morbidity*

Permeability Ratio	No. in Group	Influenza	Scarlet Fever	Typhoid	Diphtheria
0.57	6	1	..	..	2
0.59	2	1	..	1	..
0.60	2	1	1	..	..
0.61	3	2	..	1	2
0.62	2	1	..	1	..
0.63	5	1	..	..	..
0.64	3	..	1	..	..
0.65	6	..	..	..	..
0.66	3	3	2	..	..
0.67	2	2	2	..	..
Total.....	34	12	6	3	4
0.68	3	1	1	..	..
0.69	1	..	..	1	..
0.70	6	4	1	..	1
0.71	1	1	..	..	..
0.72	3	2	1	1	1
0.72	3	3	1	..	1
0.74	6	4	1	..	1
0.75	2	1	..	..	1
0.76	1	1	1	..	..
0.77	2	1	1	..	..
0.79	1	1	1	..	..
0.80	1	1	..	..	..
0.82	1	1	..	..	..
0.84	1	..	1	..	..
Total.....	66 (students)	21	9	2	5

Thirty-three have had influenza; fifteen have had scarlet fever; five have had typhoid, and nine have had diphtheria.

Of the thirty-four below the average (0.68) permeability, 35 per cent had influenza, while 65 per cent of the group above the average had influenza.

A striking difference is immediately apparent. The permeable students react with an increase of from 30 to 55 per cent, reaching a maximum no later than 30 minutes after subcutaneous injection. The impermeable students, on the other hand, have a much lower curve and the maximum in two instances is reached five minutes later. In each group one student is exceptional: in the permeable group, student 65, with a permeability ratio of 82 (potassium-calcium ratio 1.5) gives an absolutely straight line. This is our "vagotonic" student. In the impermeable group, student 12 reacts with a slight fall in the rate (permeability 61, potassium-calcium ratio 1.9).

Our interpretation is the following: In the permeable group the epinephrine is promptly absorbed and the effect on the blood pressure

and pulse rate is immediately apparent. As contrasted to the impermeable group, these students are, however, relatively vagotonic, because the local constriction of the capillaries has not caused a complete anemia and the interference with absorption entailed thereby, nor has the effect on the capillary wall itself (of the lymphatics) been sufficiently great to prevent absorption.

In the impermeable group, on the other hand, the absorption is exceedingly slow and the effect negated, not because the sympathetic system is relatively inactive but because the local sympathetic tonus is much greater. In student 12, with apparent vagotonic effect, absorption is evidently of so small a degree that the autonomic nervous system in its overcorrection to minute doses, responds with an apparent vagus effect. We have repeatedly met with such results in dogs when epinephrine is administered in oil (with a slow rate of absorption). Under such circumstances actual salivation occasionally follows epinephrine injection.[15]

In both these students we injected epinephrine intravenously (charts 2, 3 and 4) and plotted the systolic and diastolic pressure and pulse rate for both subcutaneous and intravenous injection. The dose was, however, not alike in the two students. The "vagotonic" student (student 65) was given 4 minims of a 1 : 1,000 solution, the sympathetic (student 12) 1 minim. The results are of interest from a clinical standpoint because of the frequency with which subcutaneous injections are made to determine the relative reactivity of the autonomic apparatus, and interpretations made without due consideration of the local factors involved.

Ionic Equilibrium of the Blood.—We wish finally to present the results of blood analyses made on twenty-three of the men. These students were selected as representatives of different degrees of reactivity.

In table 6 we present them according to the permeability.

It will be noted that the potassium-calcium ratio of the permeable group is decidedly lower than that of the less permeable groups. There are, however, some striking exceptions of impermeable students with relatively low ratios, for example, students 11, 12 and 32.

When we now examine the same groups arranged on the basis of the inflammatory index the correlation to the blood chemistry is apparent.

From these tables it is probable that we may have relatively impermeable capillaries with a low potassium-calcium ratio, but in general increased capillary permeability parallels the lowering of the potassium-calcium ratio.

It is only when we examine the classification according to inflam-

15. Petersen, W. F.: To be published.

matory index that the agreement becomes quite regular. Here there is a progressive increase in the inflammatory reactivity as the ratio becomes smaller.

We should like to emphasize these findings because of considerable confusion that exists in the interpretation of many investigations of blood calcium values.

It will be observed that there is little or no difference in the actual calcium values of the serum. The marked difference exists in the potassium values. In the impermeable group we find relatively much potassium in proportion to the calcium. This means that the condition as far as the cells are concerned is the reverse, with more calcium and less potassium in proportion. This is in agreement with what is known of the general protoplasmic effect of calcium and potassium on cellular

TABLE 6.—*Relation of Permeability to Potassium-Calcium*

Student	Permeability Ratio	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Potassium / Calcium
2	57	10.00	19.5	1.95
4	57	9.82	25.5	2.60
6	57	10.00	25.8	2.58
9	60	8.92	22.1	2.50
10	60	10.26	21.0	2.00
11	61	10.00	18.7	1.87
12	61	10.26	19.8	1.90
17	63	9.48	25.5	2.50
18	63	9.14	24.6	2.70
21	64	9.90	21.5	2.00
25	65	9.48	26.0	2.70
Averages (11)	60	9.74	22.7	2.30
30	66	9.65	27.40	2.80
32	66	10.40	18.74	1.80
34	67	10.08	19.60	1.94
36	68	9.48	25.60	2.80
41	70	9.65	24.60	2.50
82	70	10.00	23.00	2.30
Averages (6)	68	9.87	23.1	2.34
54	74	9.35	17.35	1.90
59	75	10.00	19.03	1.90
62	77	9.90	17.10	1.72
64	80	10.26	17.30	1.60
65	82	10.08	15.05	1.50
66	84	10.08	17.61	1.76
Averages (6)	78	9.94	17.20	1.72

activity. In the group with high inflammatory index (increased permeability, short blister time) we have in the serum a larger proportion of calcium to potassium, and the cells will contain little calcium as compared to the potassium.

CHILDREN

We have had but few children in our series of normals; the group is tabulated in table 8.

In general the permeability ratio is higher than in our adult group and the blister time shortened. On the other hand, the assumption that

in infants this might be true to an even greater degree seems fallacious, for in the two cases that we have been able to observe the infant of 7 days (normal) had a ratio of only 0.63, and a three months' feeding infant a ratio of 0.74. It is to be remembered that the skin capillaries of the infant under three months differ materially in their anatomic structure from those of the normal adult.

TABLE 7.—*Relation of Inflammatory Index to Potassium-Calcium Ratio*

Student	Inflammatory Index	Potassium / Calcium	Blister Time in Hours
6	3.5	2.58	16
30	6.6	2.80	10
10	6.7	2.00	9
12	7.1	1.90	8½
32	7.3	1.80	9
9	7.4	2.50	8
41	7.7	2.50	9
4	8.1	2.60	7
36	8.5	2.70	8
17	9.0	2.50	7
18	9.0	2.70	7
Averages (11)	7.35	2.40	9
2	9.5	1.95	6
34	9.6	1.94	7
82	10.0	2.30	7
21	10.6	2.00	6
25	10.8	2.70	6
66	12.0	1.76	7
Averages (6)	10.4	2.11	6.6
59	15.0	1.90	5
11	15.20	1.87	4
62	17.0	1.70	4½
64	17.7	1.60	4½
65	18.2	1.50	4½
54	18.5	1.90	4
Averages (6)	17.0	1.74	4½

TABLE 8.—*Normal Juvenile Group*

Number	Sex*	Race	Age	Clinical Diagnosis	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
129	♀	W	7	Normal strabismus	6	8.60	6.75	0.78	13.0
128	♀	W	8	Normal strabismus	6½	8.40	6.81	0.81	12.4
126	♀	W	14	Normal; lipoma of eyelid	4½	8.28	6.80	0.82	18.2
237	♀	W	11	Elbow dislocation 2 months before examination	5	7.85	6.10	0.77	15.4
224	♂	W	12	Circumcision (24 hours previously)	5½	7.63	6.30	0.82	15.0
145	♂	W	14	Phymosis; hernia	5	7.85	5.29	0.67	13.4
146	♀	W	16	Ingrown nail	4½	7.52	5.39	0.71	15.5
179	♀	W	21	Normal (before removal of small scar)	5	7.20	5.40	0.75	15.0
B1	♀	W	7 days		6½	7.73	4.89	0.63	10.0
B.f.	♂	W	3 mo.	Feeding case	8	5.68	4.27	0.74	9.2

* In this table, ♂ indicates male, ♀ female.

SUMMARY

1. From the results obtained with the blister method we have reached the conclusion that it offers a relatively simple method of obtaining information concerning the constitutional reactivity of the individual.

2. (*a*) The permeability is determined by comparing the amount of protein in the blister to the serum protein. (*b*) The degree of inflammatory reactivity (inflammatory index) is expressed by the quotient $\frac{\text{permeability ratio}}{\text{blister time}}$.

3. In a group of sixty-six normal students examined, the permeability ratio varied from 57 to 84, the inflammatory index from 3.5 to 18.5. Averages were 68 and 10.5, respectively.

4. In the relatively impermeable group are the university athletes and sensitized individuals; in the permeable group, the majority of students who have some evidence of kidney disturbance.

5. Examined on the basis of inflammatory reactivity, the students who have had more than the average amount of parenchymal tuberculosis are low (sympathetic), as are also the students with kidney disturbance (sympathetic tonus of arterioles, increased permeability of capillaries).

6. There is definite relation between the blood pressure and permeability.

7. There is some evidence of relationship between influenza morbidity and permeability (increased permeability following influenza and scarlet fever [?]).

8. Students in the impermeable group respond to subcutaneous epinephrine injection with less systemic vascular effect (greater local effect at site of injection).

9. There is a direct chemical basis for the differences in permeability and inflammatory response, namely, the ratio of calcium and potassium. A low inflammatory index is associated with a high blood potassium-calcium ratio, a high inflammatory index with a low potassium-calcium ratio. In the tissue cells these conditions will be reversed. The impermeable cell has in general a greater amount of calcium in proportion to the potassium, while the permeable cell has a small amount of calcium to the potassium.

10. In infants the permeability of the skin capillaries is probably not high, but in children the permeability seems definitely increased over that of the adults.

Book Reviews

THE PRINCIPLES AND PRACTICE OF ENDOCRINE MEDICINE. By WILLIAM NATHANIEL BERKELEY, PH.D., M.D. Pp. 368, with index; 60 illustrations. Price, $4.50. Philadelphia: Lea and Febiger, 1926.

"The book is primarily meant for doctors in active practice. The standpoint of the writer is that of the clinical practitioner" (preface). The book contains three introductory chapters, one on general methods, one on the autonomic nervous system, and one on basal metabolism. Then follows the usual chapters on the thyroids, the parathyroids, the hypophysis, the suprarenals, the pancreas, the sex glands, the pineal body, the thymus, the intestinal mucosa and mammary glands. There is one chapter on the interrelation of the glands of internal secretion, and one on forms of pluriglandular disease, and a final chapter on endocrine influence on growth, old age and obesity.

The author has a clear and concise style. His meaning is at no time obscure. He has a good acquaintance with the great mass of scientific facts, and in most instances these are presented fairly and critically. He shows less critical discrimination in the fields in which in earlier years he had personal contact with experimental work. The different chapters are therefore of unequal reliability and value as guides for the general practitioner. The author is at his best on the thyroids, the suprarenals and the sex glands. The chapter on the pineal body is in length out of all proportion to what is known concerning the rôle of this body in health and in disease. But here, as in some other cases, the author has something to sell: a pineal extract which when given by mouth to "backward" children for a long time is said to improve the mentality.

Some of the faulty or inadequately qualified statements of facts may be noted. The author seems not acquainted with the numerous reliable researches that show no direct influence of sympathetic nerves on the tonus of skeletal muscles (pp. 30, 31 and 143). He states that thyroidectomy in rabbits is without effect (p. 42). This is contrary to fact. "Marine's statement that the immediate cause of goiter (simple) is lack of iodine can hardly be affirmed any more than it can be claimed that the immediate cause of malaria is lack of quinine" (p. 63). This is a curious lack of understanding and logic in a man who at times shows the fallacy of "the undistributed middle" in the argument of others. Quinine appears to be a direct germicide, and not as iodine, a necessary element in the structure of an important hormone.

Speaking of his own parathyroid preparation administered by mouth, he reports "remarkable benefits" in the majority of cases of paralysis agitans, despite the improbability of parathyroid origin of this malady, and the indication that the parathyroid hormone is ineffective by the oral route. Showing good judgment in other matters, when it comes to his own parathyroid preparation he accepts support by the ordinary testimonial route: "The wife of another recent patient writes, 'We are greatly encouraged and hope he will be entirely well.'"

"Primary anterior lobe deficiencies of a 'functional,' or at least temporary and curable character, in boys and girls of the infantile type . . . . a long series of New York Public School children of this character have passed through my hands . . . . in the last fifteen years. They receive whole pituitary (special formula prepared for me by a New York wholesaler) in suitable doses, and in the course of one or two years they grow remarkably" (p. 188). We have the right to ask how much did the *control* group of similarly "temporary" infantile children grow in the same length of time?

"In the treatment of Froelich's disease the prolonged administration of whole pituitary gland preparation is the most rational procedure" (p. 195), despite the evidence (Evans, Smith and others) that anterior lobe hormone is ineffective by the oral route.

On page 261 he states that in diabetes he still "with satisfaction" uses his own extract of the pancreas given by mouth, despite the evidence that insulin, except in enormous quantities, is ineffective by that route.

"Ligation or partial excision of the vas deferens causes a slow atrophy of the seminiferous cells" (p. 271). This has been disproved by Moore and others.

"A high degree of sexual ardor at the time of intercourse probably modifies favorably the growth if not the structure of the fertilized ovum" (p. 295). The evidence for this is cited from King Lear.

The author recommends pluriglandular therapies. "In all cases of depressed metabolism, retarded sex development and diminished growth, thyroid and anterior pituitary and probably pineal will act act synergically" (p. 344).

"In frank cretinism it has seemed to me useful to supplement the action of the thyroid with whole pituitary, pineal, and the proper gonad. When the patient is carefully watched pluriglandular therapy can at least do no harm" (p. 345). The last statement is probably true in regard to the patient's body, but what about the patient's pocketbook and the physician's mind?

The same kind of therapy is recommended in so-called endocrine obesity. "It may even be well to give thyroid, pituitary and ovarian (or testis) extract in one pill . . . . The food supply should be slowly diminished and this medication slowly discarded until the patient loses 1½ to 2 per cent of his body weight per month" (p. 356). Why reduce the food supply if the obesity is of endocrine origin and curable by feeding endocrine mixtures? By speeding up metabolism, increasing nervous tension, and increasing the energy expenditure in muscular work, thyroid extract will by itself reduce body weight in obesity, even on a uniform intake of food.

The book is written from the standpoint of the clinical practitioner for physicians in active practice. But curiously enough, the author shows greater erudition, critical judgment and common sense in the presentation of the experimental data than in the presentation of the clinical data. The volume is therefore a "mixed blessing" in this era of mushroom growths of monographic endocrinology.

LE TERRAIN HEREDO-SYPHILITIQUE. By V. HUTINEL, Professeur honoraire de clinique medicale infantile et Membre de l'Academie de Medicine. Pp. 455. Paris: Masson et Cie, 1926.

The present volume is the product of the ripe experience of an eminent French pediatrician and syphilologist. On page 89 he says: "When I was an intern to Parrot in 1876 . . . . ." An internship with Parrot and fifty years of experience make an interesting introduction, and one is not disappointed. The book is not a compilation and is therefore not burdened with references. It is the statement of a man who knows congenital syphilis in all its manifestations from personal observation under most favorable circumstances, and over a period of many years, and who has lost none of the vigor and enthusiasm of youth in the presentation. I know of no treatise on congenital syphilis in any language that presents the whole subject so exhaustively, so satisfactorily, so authoritatively, so systematically, and so fascinatingly. It is the sort of a book in a short review of which it is hard to know what phase to bring into relief. One cannot help, however, emphasizing as an illustration the eighteen page chapter on "l'appareil urinaire"—a convincing first hand presentation that I am sure is a revelation to most, if not indeed all, of us. The same could be said of many other chapters. The book can be warmly commended to both the pediatrician and the syphilologist, both because it is a most satisfactory treatise in itself and because it has that added value and interest that always attach to the personal views and presentation of a master clinician. The book must be read to be appreciated.

LES MALADIES DES GLANDES ENDOCRINES. By PROF. KNUD H. KRABBE. Pp. 92; 25 illustrations. Paris: Librairie le François, 1926.

This little volume is a translation into French of the chapter by Krabbe on the diseases of the endocrine glands in the Danish Laerebog intern Medicin (Copenhagen, 1922). There are twenty-five well selected photographic illustrations. The book is a concise and conservative summary of the present status of our knowledge as to symptoms, diagnosis and therapy of the disorders of the thyroids, the parathyroids, the pituitary, the pineal, the thymus, the pancreas, the suprarenals and the gonads. The last chapter is devoted to some disorders in which endocrine involvement is in doubt, such as mongolism, infantilism and osteomalacia.

THE INTERNATIONAL MEDICAL ANNUAL: A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX. FORTY-FOURTH YEAR, 1926. Cloth. Price, $6. Pp. 555, with illustrations. New York: William Wood & Co., 1926.

We have yet to see a volume of this annual that was not good. It is remarkable to note as we go through this book how thoroughly and carefully recent literature is reviewed and digested. And the annual really is international.